DISSERTATION ON

A STUDY OF NEONATAL SEIZURES IN VIEW OF PRESENTATION, ETIOLOGY, ONSET AND CLINICAL MANIFESTATION

Dissertation Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations

for the award of the degree of

M.D IN PAEDIATRIC MEDICINE

BRANCH VII

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CERTIFICATE

I certify that the dissertation titled **"A STUDY OF NEONATAL SEIZURES IN VIEW OF PRESENTATION, ETIOLOGY, ONSET AND CLINICAL MANIFESTATION"**, submitted by **Dr. DIVAKAR .R,** for the Degree of DOCTOR OF MEDICINE (PAEDIATRICS) (BRANCH VII), to The Tamil Nadu Dr.M.G.R. Medical University, Chennai, is the result of original research work undertaken by him in the Department of Paediatrics, Thanjavur Medical College, Thanjavur.

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DECLARATION

I hereby solemnly declare that the dissertation titled "**A STUDY ON CLINICAL PROFILE OF MECONIUM ASPIRATION SYNDROME IN RELATION TO GESTATIONAL AGE AND BIRTH WEIGHT AND THEIR IMMEDIATE OUTCOME**" has been prepared by me under the guidance of **PROF.DR.M.SINGARAVELU.MD.,DCH.,DNB(peds).,MNAMS** PROFESSOR AND HOD, DEPARTMENT Of PAEDIATRICS, THANJAVUR MEDICAL COLLEGE, THANJAVUR. This is submitted to THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY, CHENNAI, in partial fulfillment of the requirement for the degree of DOCTOR OF MEDICINE (PAEDIATRICS) (BRANCH VII).

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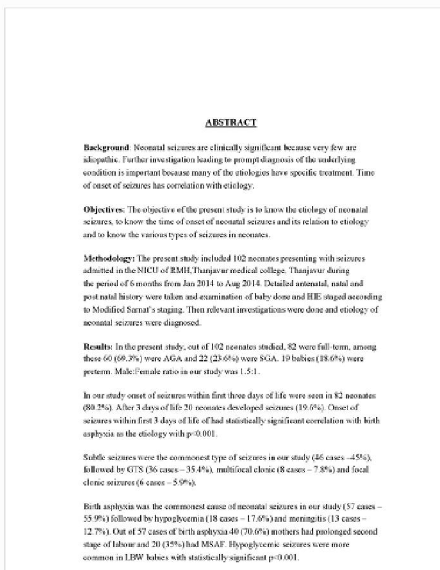


ABSTRACT

Background: Neonatal seizures are clinically significant because very few are idiopathic. Further investigation leading to prompt diagnosis of the underlying condition is important because many of the etiologies have specific treatment. Time of onset of seizures has correlation with etiology.

Objectives: The objective of the present study is to know the etiology of neonatal seizures, to know the time of onset of neonatal seizures and its relation to etiology and to know the various types of seizures in neonates.

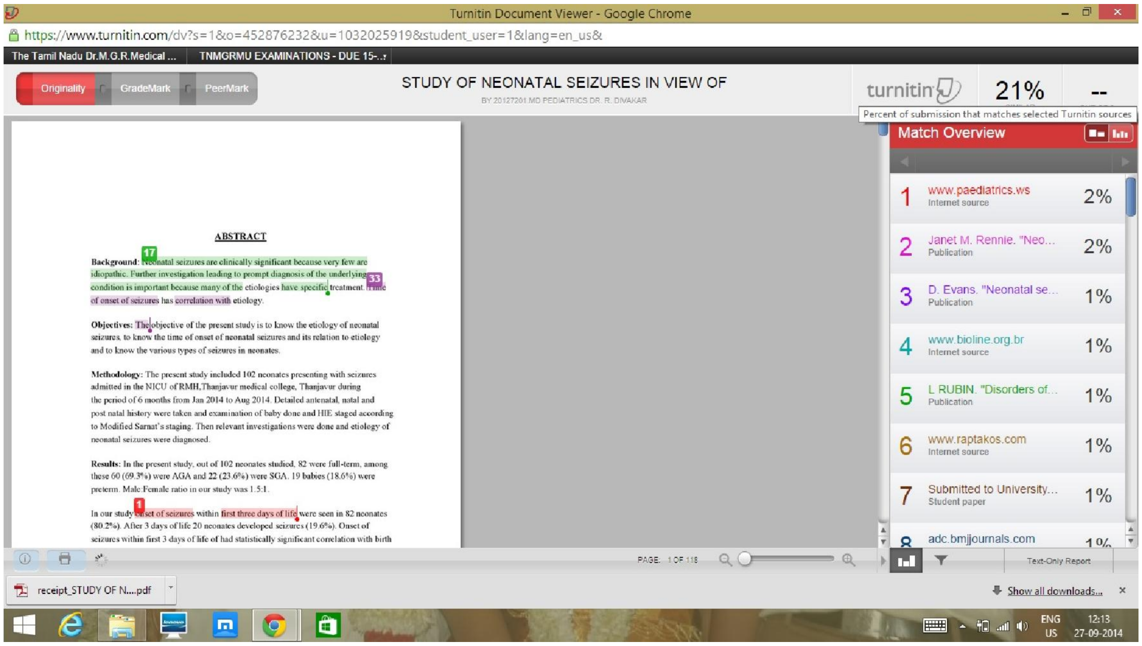
Methodology: The present study included 102 neonates presenting with seizures admitted in the NICU of RMH,Thanjavur medical college, Thanjavur during the period of 6 months from Jan 2014 to Aug 2014. Detailed antenatal, natal and post natal history were taken and examination of baby done and HIE staged according to Modified Sarnat's staging. Then relevant investigations were done and etiology of neonatal seizures were diagnosed.

Results: In the present study, out of 102 neonates studied, 82 were full-term, among these 60 (69.3%) were AGA and 22 (23.6%) were SGA. 19 babies (18.6%) were preterm. Male:Female ratio in our study was 1.5:1.

In our study onset of seizures within first three days of life were seen in 82 neonates (80.2%). After 3 days of life 20 neonates developed seizures (19.6%). Onset of seizures within first 3 days of life of had statistically significant correlation with birth asphyxia as the etiology with $p<0.001$.

Subtle seizures were the commonest type of seizures in our study (46 cases –45%), followed by GTS (36 cases – 35.4%), multifocal clonic (8 cases – 7.8%) and focal clonic seizures (6 cases – 5.9%).

Birth asphyxia was the commonest cause of neonatal seizures in our study (57 cases – 55.9%) followed by hypoglycemia (18 cases – 17.6%) and meningitis (13 cases – 12.7%). Out of 57 cases of birth asphyxia 40 (70.6%) mothers had prolonged second stage of labour and 20 (35%) had MSAF. Hypoglycemic seizures were more common in LBW babies with statistically significant $p<0.001$.



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LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

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Objectives: The objective of the present study is to know the etiology of neonatal seizures, to know the time of onset of neonatal seizures and its relation to etiology and to know the various types of seizures in neonates

Methodology: The present study included 102 neonates presenting with seizures admitted in the NICU of RMH, Thanjavur Medical College, Thanjavur, during the period of 8 months from Jan 2014 to Aug 2014. Detailed antenatal, natal and post natal history were taken and examination of baby done and HIE staged according to Modified Sarnat's staging. Then relevant investigations were done and etiology of neonatal seizures were diagnosed.

Results: In the present study, out of 102 neonates studied, 82 were full-term, among these 60 (58.8%) were AGA and 22 (21.6%) were SGA. 19 babies (18.6%) were preterm. Male: Female ratio in our study was 1.5:1.

Conclusion: The recognition of etiology of neonatal seizures is often helpful with respect to prognosis and treatment. The most common etiology for neonatal seizure is HIE and is frequently associated with perinatal risk factors. Onset of seizures during first 3 days of life has significant correlation with HIE as etiology.

Hypoglycaemic seizures are more common in LBW babies.

Subtle seizures are commonest type of clinical seizures, which is difficult to identify, therefore careful observation of at risk neonates is necessary.

Keywords:

Neonatal seizures; Birth asphyxia; HIE; Subtle seizures; Hypoglycemia.

In our study onset of seizures within first three days of life were seen in 82 neonates (80.2%). After 3 days of life 20 neonates developed seizures (19.6%). Onset of seizures within first 3 days of life of had statistically significant correlation with birth asphyxia as the etiology with $p<0.001$.

INTRODUCTION

Seizures represent the most distinctive signal of neurological disease in the newborn period. The convulsive phenomenon are the most frequent of the overall manifestation of neonatal neurological disorders.

Neonatal seizures are common and may be the first manifestations of neurological dysfunction after a variety of insults. Neonatal seizures are clinically most important sign to be recognized.

It is critical to recognize neonatal seizures to determine their etiology and to treat them for 3 major reasons:

1. First, seizures are usually related to significant illness, sometimes requiring specific therapy.
2. Second, neonatal seizures may interfere with important supportive measures, such as alimentation and assisted respiration for associated disorders.
3. Third, experimental data give reason for concern that the seizures per se may be a cause of brain injury.

Neonatal seizures present with varying manifestations like generalized tonic, multifocal clonic and subtle activity. Therefore it is important to recognize the seizures and treat it, as delay in recognition and treatment may lead to brain damage.

The time of onset of seizure has relationship with the etiology and prognosis. For example, birth asphyxia usually presents in the first three days of life whereas meningitis presents after first week. If baby convulse within hours of delivery, it signifies poor prognosis and brain damage

Taking above points into consideration, the study of etiology, onset and clinical manifestations of neonatal seizures has a significant role.

AIMS & OBJECTIVES

1. To study the etiology of neonatal seizures.

2. To study the time of onset of neonatal seizures and its relationship with the etiology.

3. To study the various types of presentation of seizures in neonates significant because very few are idiopathic.

REVIEW OF LITERATURE

Historical Review:

Epilepsy was known to ancient Babylonians and was described by Hippocrates, who considered it as disease of brain. Its history related by Temprin, Spans that of medicine itself. Hughlings Jackson described seizure as "excessive discharge of nerve tissue on muscle". Jackson went on to say that this discharge occurs in all degrees, it occurs with all sorts of conditions of ill health, at all ages and under innumerable circumstances. These observations by Jackson remain as true today as they did 130 years ago.

Von Rosentein in 1776 stated that "Lastly we may observe, to the great comfort and satisfaction of the parents of those young children subject to convulsion or the epilepsia infantilis, that they need not be apprehensive for its changing into the true epilepsy, for it generally disappear by degree, as they grow older and acquire more strength".

The great Swedish Proto Pediatrician Von Rosenstein in his rather optimistic prognosis for early convulsions, showed remarkable insight not only into the concern of parents, but also into the tendency towards spontaneous improvement. He clearly recognized the distinction made between those young children, who are subjected to seizures for a limited period and those who show tendency to recurrent attacks somewhat late, justifying the use of the word epilepsy.

Epilepsy is the expression of occasional sudden excessive rapid local discharge in the grey matter is of little practical use to pediatricians involved in the problem of seizures. The discharge may result in an almost instantaneous loss of consciousness, alteration of perception or impairment of psychic function, convulsive movements, disturbance of sensation or some combination thereof.

A terminologic difficulty arises from the diversity of clinical manifestations. The term convulsion, referring as it does to an intensive paroxysm of involuntary repetitive muscular contractions, is inappropriate for a disorder that is known as an alteration of sensation or consciousness. Seizure is preferable as a generic term, since it enhances the diversity of paroxysmal events and also for the reason that it tends itself to qualification.

A clinical seizure is a sudden paroxysmal depolarization of a group of neurons that results in a transient alteration in neurological state. This may involve abnormal motor, sensory or autonomic activity with or without change in the conscious level.

A seizure includes clinical phenomena that are temporally associated with EEG seizures activity and therefore are clearly epileptic. The definition also includes paroxysmal clinical phenomenon that often are most associated temporally with EEG seizure activity.

Seizures in the newborn are identified by direct clinical observation. However, the findings of a series of studies performed largely on the past several years by EEG monitoring with simultaneous direct clinical observation, raise two important possibilities about clinically identified neonatal seizures. First, some clinically identified motor and behavioural phenomenon characterized as seizures do not have a simultaneous EEG seizure correlate i.e., the number of certain seizures may have been over-estimated in the past. Second, many EEG seizures are not accompanied by clinically observable alterations in neonatal motor or behavioural function, i.e., the total number of neonatal seizures may have been under-estimated in the past. The revised classification of neonatal seizures by JJ Volpe were based on above findings.

A seizure may arise from varying foci at different times. Not all clinical seizures are correlated with EEG changes and not all seizures shown on EEG recordings are clinically apparent.

Pathophysiology:

The neonatal brain appears uniquely susceptible to seizures. Neonatal GABA receptors are excitatory and are functionally more active than N-acetyl-d-aspartate receptors at this time of life. There is now convincing evidence that neonatal seizures have an adverse effect on neurodevelopmental outcome in later life. Animal studies have shown that seizures impair neurogenesis and derange neuronal structure, function and connectivity. The hippocampus has been well studied, because it is particularly susceptible to seizure induced injury. Seizures cause synaptic reorganization with aberrant growth of dentate granule cell axons. There is also apoptosis in the inner granule cell layer of the dentate hilus and bilateral hippocampal sclerosis has been seen at autopsy in human babies who suffered prolonged seizures.

Seizures lead to mismatch between energy supply and demand and although there is a rise in cerebral blood flow, this may not be sufficient to meet the requirements. Neonates have a low cerebral metabolic rate and a fragmentary neuronal network, making them less vulnerable to neuronal damage and cell loss than adults and more resistant to toxic effects of glutamate. However seizures can undoubtedly inhibit brain growth, modify neuronal circuit and increase neuronal excitability.

Recurrent seizures during early development have been shown to result in impairment of visual spatial learning and memory. Status epilepticus and recurrent seizures have also been shown to predispose the brain to seizures in later life. Magnetic resonance spectroscopy studies show areas of cerebral metabolic dysfunction resulting in necrotic damage to the thalamus in immature rats.

Epidemiology:

The incidence varies from 1.5-3.7/1000 live births in term babies and 6-12% in babies weighing less than 1500gram.

Types of Seizures:

The identification of seizures presents a significant clinical problem in caring for neonates. They are difficult to recognize and consequently the determination of etiology and the initiation of appropriate therapy may be delayed.

Four essential seizure types can be recognized in neonates according to Volpe JJ08 i.e., (1) Subtle; (2) Clonic; (3) Tonic and (4) Myoclonic. Multifocal refers to clinical activity that involves more than one side, is asynchronous and usually is migratory, whereas generalized refers to clinical activity that is diffuse bilateral, synchronous and non-migratory.

Classification of Neonatal Seizures:

Table-1: Classification of Neonatal Seizures

Clinical seizure	Electrographic Seizure	
	Common	Uncommon
Subtle	+	
Clonic		
Focal	+	
Multifocal	+	
Tonic		
Focal	+	
Generalized		+
Myoclonic		
Focal, multifocal		+
Generalized	+	

Subtle Seizures:

This is the most common type of neonatal seizures. Available information from studies using EEG simultaneously with slow recording or direct observation suggest that:

1. Subtle seizures are more common in premature infants.
2. Many subtle clinical phenomenon in full term infants are not consistently associated with abnormal EEG discharge.

Eye opening, ocular movements, peculiar extremity movements (resembling boxing or hooking movement), mouth movements and apnea have been documented in association with EEG seizure activity, usually in temporal leads.

In study of Mizrahi and Kellaway9, 22 infants of which 19 (85%) were more than 36 weeks of gestation exhibited paroxysm of ocular movements such as eye blinking, oral buccal lingual movements, pedalling or stepping movements or rotatory arm movements with an inconsistent association with EEG seizure activity.

The data appear to indicate that much caution should be used in attributing an epileptic origin to many subtle clinical phenomenon, particularly in full-term infant and particularly if these phenomenon are the only manifestation of seizure in the infant. Although apnea has been demonstrated as a seizure manifestation in the premature newborn, vast majority are non-epileptic in origin. In 14 of the 21 infants studied by Watanabe et al10 the infants exhibited other subtle phenomenon during the apneic seizure e.g., staring, mouth movements. Apnea as a seizure with EEG activity is less likely to be associated with bradycardia than is non-convulsive apnea.

Clonic:

Clonic seizures represent the seizure type associated most consistently with EEG seizure activity. Clonic movements in the newborn are rhythmic and usually rather slow. It is categorized into focal or multifocal. Focal clonic seizure involves face, upper and/ or lower extremities on one side of the body or axial structures on one side of the body. Infants commonly are not clearly conscious during or after the focal seizures and the neuropathology is often focal in nature e.g., cerebral infarction. However, it is important to recognize that focal clonic seizures may occur with metabolic encephalopathies in the newborn.

Multifocal clonic seizures involve several body parts, often in migration fashion, although the migration most often "marches" in a non-Jacksonian manner.

Tonic:

Tonic seizures are clinical episodes most common of which are not unassociated with time-synchronized EEG discharges. Two categories of tonic seizures should be distinguished i.e., focal and generalized. The latter are much more common than the former. Focal tonic seizures consists of sustained posturing of the limb or asymmetric posturing of the neck or trunk. In contrast to generalized tonic seizures, focal are consistently associated with EEG activity.

GTS are characterized most commonly by tonic extension of both upper and lower extremities, and also by tonic flexion of upper limb with extension of lower limb. Approximately 85% of such clinical seizures were not accompanied by electrical seizure activity.

Myoclonic Seizures:

Myoclonic seizures are clinical episodes that as a group are most commonly unassociated with time synchronized EEG discharges. Myoclonic movements are distinguished from clonic because of the more rapid speed of myoclonic jerk and particular predilection for flexor muscle groups. Three categories should be distinguished (1) focal (2) multifocal (3) generalized. Focal myoclonic type typically involve flexor muscles of an upper limb. Out of 41 focal myoclonic seizures studied by Mizrahi and Kellaway9, only 3 were associated with EEG seizure discharges.

Multifocal myoclonic are characterized by asynchronous twitching of several parts of the body. Generalized myoclonic seizures are characterized by bilateral flexor jerks of upper limb and lower limb and are more likely to be associated with EEG seizure discharge. Of 58 generalized myoclonic seizures studied by Mizrahi and Kellaway9, 35 had EEG seizure discharge.

Seizures versus Jitteriness and other non-Epileptic Movements:

Jitteriness, although not a type of seizure, is a movement disorder that is often confused with seizure. It is characteristically a disorder of the newborn and is seen rarely, if ever, in similar form at a later age. Jitteriness is characterized by movements with qualities primarily of tremulousness but occasionally also of clonus. Distinguishing jitteriness from seizure is readily done at the bedside, if the following five points are remembered:

Table-2: Difference between jitteriness and seizures in neonates

Sl.	Clinical Features	Jitterines	Seizure
1.	Abnormality of gaze or eye	0	+
2.	Movements, exquisitely stimulus	+	0
3.	Predominant movement	Tremor	Clonic jerking
4.	Movements cease with passive	+	0
5.	Autonomic changes	0	+

The most consistently defined causes of jitteriness are HIE, hypocalcaemia, hypoglycemia and drug withdrawal. It should be noted that the distinguishing clinical features described above are useful in the clinical distinction of episodic movements other than jitteriness that might be confused with an epileptic seizure. Of particular importance is the increase of non-epileptic movements with sensory stimulation, their suppression with gentle restraint and their lack of accompaniment by metabolic changes.

Finally it is important to recognize that newborns exhibit normal motor activity that could be mistaken for seizure. Awareness of such normal activity should allow ready distinction from seizure at bedside.

Neonatal Motor Activity commonly mistaken for Seizures:

Awake or Drowsy:

- Roving, sometimes dysconjugate eye movements.
- Sucking, puckering movements not associated by ocular phenomenon.

Sleep:

- Fragmentary myoclonic jerk
- Isolated, generalized myoclonic jerk as infant wakes from sleep.

Of all the seizures in neonates, subtle seizure is the commonest in majority of the studies. In a study of neonatal seizures by Brunquell Philip J et al[12] subtle seizures were the commonest seen in 51% (27 out of 53), followed by focal clonic seen in 42%(22 out of 53), multifocal clonic seen in 30% (16 out of 53) and generalized tonic in 23%(12 out of 53). In a study by Lakra Mahaveer et al [13] subtle seizures were the commonest seen in 52 out of 93 cases (56.98%) followed by focal clonic seen in 21 out of 93 cases(23%) and multifocal clonic seen in 18 out of 93 cases (19.35%).

Etiology of Neonatal Seizures:

The etiology of neonatal seizures is multiple and diverse and has evolved significantly over the last two decades. In the past cause was undetermined in approximately one-third of infants presenting with neonatal seizures. Recent neuroimaging technology has allowed for the detection and definition of neuropathologic changes increasing the diagnostic acumen.

In addition, improvements in neonatal intensive care have decreased mortality rates. Severely ill newborn infants with multisystem disease now survive. Therefore neonatal seizures may be multifactorial, whereas electrolyte disturbances, acute trauma and bacterial infections of the CNS were frequently causative in the past, HIE, cerebrovascular disease and cerebral malformation are more frequently diagnosed today.

Early onset seizures occur in HIE, ICH and metabolic causes. Later, onset seizures occur with metabolic disease and drug withdrawal, but more frequently with intracranial infections. Intractable or protracted seizures, despite anti-convulsant therapy occur most often with HIE. Following are the common causes of neonatal seizures and are listed below.

1. Hypoxic ischemic encephalopathy
2. Intracranial hemorrhage(ICH)
    - Intraventricular hemorrhage(IVH)
    - Subdural hemorrhage(SDH)
    - Subarachnoid hemorrhage(SAH)
    - Parenchymal hemorrhage
3. Central nervous system infections:
    - Intrauterine
    - Postnatal
4. Congenital malformations:
    - Induction anomalies
    - Migration anomalies

4. Cerebrovascular syndrome
    - Cerebral infarction
    - Vascular infarction
5. 6. Metabolic:
    - Electrolyte and chemical abnormalities
    - Neurometabolic disorders
6. 7. Drug withdrawal and toxins
7. 8. Benign neonatal seizures.

The most important etiologies and their usual time of onset are shown below:

First day:

HIE, Hypocalcemia, pyridoxine dependency, accidental injection of local anaesthetics.

Between 1-3 days:

ICH, hypoglycemia, inborn errors of metabolism

4th – 7th day:

Meningitis, TORCH infections, developmental malformations.

> 7 days:

Late onset meningitis, late onset hypocalcemia.

Hypoxic Ischemic Encephalopathy (HIE)

HIE is the most common cause of neonatal seizures. Perinatal asphyxia usually refers to an insult accompanied by decreased oxygen delivery to the fetal/neonatal brain. When asphyxia is followed by abnormal neonatal behaviour, a syndrome has been described known as HIE. The hypoxic ischemic insult may result from impaired placental exchange or blood flow from umbilical cord compression or may occur postnatally as a result of neonatal respiratory or cardiac compromise. Significant intrapartum asphyxia usually results in the birth of an infant with depressed cardio-respiratory function evidenced by low Apgar scores, which further compromises the hypoxic ischemic insult. Following delivery, these infants display alterations in consciousness, muscle tone and primitive reflexes, producing a recognizable syndrome.

Pathophysiology:

The relative contribution of hypoxia, ischemia and cerebral edema to brain damage in term newborns with HIE is controversial.

The systemic response to asphyxia:

The fetal circulation accommodates itself to reduction in arterial oxygen concentration by maximizing blood flow to the brain at the expense of other organs. Reduction in oxygen concentration of >90% produce brain damage and also cause cardiovascular collapse. Cerebral

Blood Flow:

The mean cerebral blood flow in normal newborn ranges from 50-60 mL/min/ 100 gm brain weight. Autoregulation of cerebral blood flow is lost in asphyxiated preterm babies. Loss of autoregulation results in a linear relationship between blood pressure and cerebral blood flow and leaves the brain vulnerable to hemorrhage and infarction when blood pressure fluctuates widely. This may be the mechanism of sub-ependymal hemorrhage and PVL in preterm newborns. A cerebral blood flow of 20 ml/min/ 100 gm brain or less results in permanent brain damage in both term and preterm newborns.

Biochemical Consequences of Asphyxia:

Brain does not adequately store energy for its own metabolism and requires a constant supply of glucose and oxygen. The diet of newborn babies is relatively rich in fats, the source of ketones. The use of ketones as a source of energy spares glucose for the synthesis of myelin lipids and other compounds.

During periods of oxygen deprivation, neither glucose, nor ketone bodies can be completely oxidized to carbon dioxide and water. Energy must be supplied by anaerobic glycolysis in which the end product is lactic acid. Brain lactate level rises, which may cause tissue destruction. The role of lactate induced cerebral edema in pathogenesis of brain damage from HIE remains controversial. However, tissue acidosis produced by lactate and carbon dioxide may also cause brain injury by impairing vascular auto-regulation inhibiting glycolysis and producing direct cell injury. The limited capacity of the white matter for compensatory hyperemia during hypoxia causes a glucose deficit relative to the excessive demands of glycolysis for energy. This deficit could result in injury to the cerebral white matter.

The most common site of abnormality in the brain of infants, especially premature ones, who die in the first three months postpartum is in the deep white matter surrounding the lateral ventricles. These lesions have been termed "perinatal telencephalic leukoencephalopathy" and consists of hypertrophied astrocytes and acutely damaged glial cells. When ischemia is added to hypoxia, brain acidosis increases.

Grossly the following lesions may be seen after moderate to severe asphyxia:

1. **Focal or multifocal cortical necrosis** with resultant cystic encephalomalacia or ulegyria (attenuation of depth of sulci) due to loss of perfusion of one/or severalvascular beds and affecting all cellular elements.
2. **Watershed infarcts**: Examples of this include periventricular leukomalacia in preterm infants, bilateral parasagittal cortical and subcortical white matter injury of term infant; and injury to pareito-occipital cortex.
3. **Selective neuronal necrosis** is the most common injury. This injury occurs at specific sites to specific cell types (neurons) e.g., hippocampus, Purkinje cells, brain stem nuclei.
4. **Status marmoratus**: Necrosis of thalamic nuclei and basal ganglia, a sub-type of selective neuronal necrosis.

Insult due to prolonged partial episodes of asphyxia e.g., abruptio placentae, causes diffuse cerebral necrosis and seizures and paresis might be expected, while acute total asphyxia (cord prolapse) seems to spare cortex and affects basal ganglia, thalamus and there is disturbance of heart rate, tone, blood pressure, cranial nerve palsies, etc.

Risk factors for HIE:

1. Prolonged 2nd stage of labour (>120 mins)
2. Chronic utero-placental insufficiency
3. Macrosomia
4. Shoulder dystocia
5. Prolonged abnormal FHR

Clinical Features:

Sarnat classified HIE in to three stages depending on the examination of the baby

Table-3: Modified Sarnat's Staging of HIE

		HIE-I	**HIE-II**	**HIE-III**
1.	Level of	Alert	Lethargic	Comatose
2.	Muscle tone	Normal	Hypotonia	Flaccid
3.	Deep tendon	Increased	Increased	Depressed/
4.	Myoclous	+	+	--
5.	Moro's response	Exaggerated	Incomplete	Absent
6.	Grasping	Normal	Exaggerated	Absent
7.	Doll's eye	Normal	Over reactive	Absent
8.	Pupils	Dilated	Constricted	Variable/ fixed
9.	Heart rate	Normal/	Bradycardia	Bradycardia
10.	Seizures	None	Common	Decerebrate/
11.	EEG	Normal	Low voltage	Isoelectric

The syndrome of HIE has a spectrum of clinical manifestations from mild to severe. In its most dramatic form, the initial phase lasts about 12 hours after the insult and consists of signs of cerebral dysfunction. The infants are stuporus/ comatose have periodic breathing/ irregular respiratory effort.

Subtle, tonic or multifocal clonic seizures occur 6-24 hours after the insult in50% of moderately to severely asphyxiated infants. Severely affected infants have progressive deterioration in CNS function over 24-72 hours following insult with coma, prolonged apnea and further brainstem dysfunction.

Other organs also display evidence of asphyxial damage. Kidneys are usually involved leading to acute tubular necrosis. Persistent oliguria (<1 ml/ Kg/hr) is significantly associated with severe HIE and a poor outcome (90%).

Intracranial Hemorrhage (ICH):

This is one of the important causes of neonatal seizures. The incidence varies from 2 to >30% in newborns depending upon the gestational age at birth and the type of ICH.

Bleeding within the skull can occur:

1. External to the brain in to epidural, subdural or subarachnoid spaces.
2. Into the parenchyma of cerebrum or cerebellum.
3. Into ventricles from the sub-ependymal germinal matrix or choroid plexus.

The incidence, pathogenesis, clinical presentation, diagnosis, management and prognosis of these hemorrhages vary according to their location, severity and the gestational age of the infant.

Diagnosis typically depends on clinical suspicion, when an infant presents with typical neurological signs, such as seizures, irritability and depressed level of consciousness and focal neurological deficits. Diagnosis is confirmed preferably with an appropriate neuro-imaging study. Management varies according to the size and location of the ICH and presenting neurological signs. Management is focused on treating complications such as seizures and post-hemorrhagic hydrocephalus.

Subdural Hemorrhage (SDH) and Epidural hemorrhage:

Etiology & Pathogenesis:

The pathogenesis of SDH relates to rupture of the draining veins and sinuses of brain that occupy the subdural space. Vertical moulding, fronto-occipital elongation and torsional forces acting on the head during delivery may provoke laceration of dural leaflets of either falx cerebri or tentorium cerebelli. This results in rupture of the veins of Galen, inferior sagittal sinus and a posterior fossa SDH. Breech presentation also predisposes to depressed fracture of the occipitalbone which may lead to rupture of the occipital sinus. SDH in the supra-tentorial space usually results from the rupture of bridging superficial veins over the cerebral convexity. Other risk factors for SDH include large head size, rigid pelvis, prolonged labour, breech, face presentation, difficult instrumental delivery, thrombocytopenia, vitamin C deficiency, hemophilia, infection or disseminated intravascular coagulation

Clinical Presentation:

When the accumulation of blood is rapid and large, as occurs with the rupture of large veins, the presentation follows shortly after birth and evolves rapidly. In infra-tentorial SDH, compression of brainstem may result in opisthotonus, coma, apnea, bulging frontanelle etc. When source of hemorrhage are small ones, there may be few symptoms or signs for up to a week, at which time either the hematoma attain a critical size, imposes on brain parenchyma and produces neurological signs or hydrocephalus develops. Seizures may occur in up to half of neonates with SDH, particularly with SDH over the cerebral convexity. With cerebral convexity SDH, there may be subtle focal cerebral signs and mild disturbance of consciousness, such as irritability, SAH probably co-exists in the majority of cases of neonatal SDH as demonstrated by CSF examination. Finally, a chronic subdural effusion may gradually develop over months, presenting as abnormal head growth in the first week to month after birth.

Subarachnoid Hemorrhage (SAH):

Etiology and Pathogenesis:

SAH is a common form of ICH among newborns. Primary SAH is probably quite frequent but clinically insignificant. Hemorrhagic/ xanthochromatic CSF may be the only indication of such a hemorrhage. The source of bleeding is usually ruptured bridging veins of the SA space of ruptured small leptomeningeal vessels. SAH should be distinguished from the subarachnoid extension of blood from germinal matrix hemorrhage/ IVH, which occur most commonly in preterm infants.

Clinical Features:

As with other forms of ICH, clinical suspicion of SAH may arise because of blood loss from other site or neurological dysfunction. More often neurological signs manifest as seizures, irritability or other mild alteration of mental status particularly with SAH or subpial hemorrhage occurring over the cerebral convexities.

Intraparenchymal Hemorrhage (IPH):

Etiology and Pathogenesis:

Primary intracerebral IPH is uncommon in all newborns, while intracerebellar IPH is found in 5-10% of autopsy specimen in the premature infant. Commonly, cerebral IPH occurs as a secondary event such as haemorrhage into a region of hypoxic-ischemic brain injury. IPH may also occur as a result of venous infarction.

Intracerebellar Hemorrhage:

Occurs more commonly in the preterm newborns and may be missed by routine cranial ultrasound. Intracerebellar IPH may be a primary hemorrhage or result from venous hemorrhagic infarction or from extension of GMH/IVH.

Clinical Feature:

The presentation of IPH is similar to that of SDH, where the clinical syndrome differs depending on whether the IPH is in the anterior or posterior fossa. In the preterm infant, IPH is often clinically silent in either intracranial fossa,unless hemorrhage is too large. In the term infant, ICH typically presents with focal neurologic signs such as seizures, hemiparesis or gaze preference along with irritability or depressed level of consciousness.

Germinal Matrix Hemorrhage/ Intraventricular Hemorrhage (GMH/IVH):

Etiology and Pathogenesis:

1. GMH/IVH is principally found in preterm infants, where the incidence is currently 15-20% in infants born <32 weeks of gestational age, but is infrequent in term newborn. The pathogenesis of IVH in the term infants is more likely to be related to trauma or perinatal asphyxia. However at least 25% of infants have no such identifiable risk factors.
2. In the preterm infants, GMH/IVH originates from the fragile involuting vessels of the subepindymal germinal matrix, located in the caudo-thalamic groove.

The risk factor are:

Intravascular:

- Ischemia/ Reperfusion e.g., volume infusion after hypotension.
- Fluctuating cerebral blood flow (e.g., with mechanical ventilation)
- Increased cerebral blood flow (e.g., hypertension, anemia)
- Increased cerebral venous pressure (high CPAP).

Vascular factors:

- Platelet dysfunction and coagulation disturbance.
- Tenuous, involunting capillaries with large luminal diameter.

Extravascular factors:

- Deficient vascular support.
- Excessive fibrinolytic activity.

Pathogenesis of complications of GMH/IVH:

There are 2 major complications:

1. Periventricular hemorrhagic infarction

2. Post-hemorrhagic hydrocephalus.

1. Periventricular hemorragic infarction:

This lesion represents a hemorrhagic venous infarction, which results from obstruction of flow in the terminal vein by large IVH. Neuropathological studies demonstrate the fan shaped appearance of a tropical hemorrhagic venous infarction in the distribution of medullary veins that drain in to the terminal veins.

2. Progressive ventricular dilatation:

May occur days to weeks following the onset of GMH/IVH. The pathogenesis likely relates to obliterative arachnoiditis that prevents CSF absorption and or obstruction of the aqueduct or the foramina of Luschka or Magendic by particulate clot. The pathogenesis of brain injury that results from post-hemorrhagic hydrocephalus is related to regional hypoxia-ischemia and mechanical distension of the periventricular white matter. In addition, the presence of non-protein bound iron in the CSF, lead to generation of reactive oxygen species, that contribute to the injury to the immature oligodendrocytes in the white matter. This results in a principally bilateral cerebral white matter injury that bears some similarity with PVL and its neuropathology and long-term outcome.

Clinical Presentation:

1. **GMH/IVH in the preterm** newborn is usually a clinically silent syndrome and thus recognized only when a routine cranial ultrasound is performed. Some infants present in hours to days with decreased level of consciousness and seizures. The only symptom showing a reliable connection with the actual time of bleeding was the appearance of seizures, which occurred in more than one-half of the infants and correlated with the isotopically estimated time of bleeding in 80% of infants. The typical seizure activity consists of rolling movements of the eyes, fist clenching, stretching of the arms and sometimes generalized tonic extension activity.

2. **The term newborn with IVH** typically presents with signs such as seizures, apnea, irritability or lethargy and a full frontanelle.

3. **Post hemorrhagic hydrocephalus** may present days to weeks following IVH and may present with increasing head growth, bulging frontanelle, splitting of sutures, decreased level of consciousness, impaired upgaze or sun setting sign, worsening respiratory status or feeding difficulties.

Metabolic Causes:

Hypoglycemia: It is one of the common causes of neonatal seizures. Hypoglycemia is more frequent in small for gestational age neonates and infant of diabetic mother. The most critical determinant for the occurrence of neurological symptoms with neonatal hypoglycemia is the duration of the hypoglycemia and the time before treatment begun.

Etiology and Risk factors:

1. Increased utilization of glucose: Hyperinsulinemia
   a) Diabetic mothers
   b) Large for Gestational Age infants
   c) Erythroblastosis
   d) Insulin producing tumors
   e) After exchange transfusion

2. Decreased production/ stores
   a) prematurity
   b) IUGR
   c) Inadequate caloric intake
   d) Delayed onset of feeding

3. Increased utilization and/ or decreased production
    a) Perinatal stress
    b) Endocrine deficiency
    c) Defects in Carbohydrate metabolism
    d) Defects in Amino Acid metabolism
    e) Polycythemia.

Clinical Features and Diagnosis:

The classic signs relate to adrenergic activation (tachycardia, sweating, and lethargy) and CNS impairment (confusion, lethargy, seizures, jitteriness). In a review of small for gestational age infants 80% had neurological symptoms and 50% experienced seizures. Onset is usually the second post natal day. In these infants it is often particularly difficult to establish that hypoglycaemia as the cause of the neurological syndrome, because perinatal asphyxia, hemorrhage, hypocalcemia and infections are frequently associated. Earlier studies showed 9% of infants with seizures as due to hypoglycemia. In recent studies, only 3% of neonatal seizures were related to hypoglycemia.

Diagnosis:

The mean glucose level during the first 3 hours after birth increased from 48 mg/dL to 70 mg/dL. In the neonate as in older children and adults, hypoglycaemia should be considered, the result of a disturbance in one or more of the metabolic hormonal systems involved in fasting homeostasis. The goal of therapy should be identical to that in older children i.e., plasma glucose more than 60 mg/dL. Plasma glucose levels of 60 to 90mg/dl should be taken as the physiologically normal optimal therapeutic range. This approximates the mean plasma glucose value found both prenatally and postnatally healthy newborns. Plasma glucose level above 40 mg/dL are not likely to be responsible for seizures, but may be suggestive of underlying abnormality. Glucose level between 40-60 mg/dL must be considered as sub-optimal. Hypoglycemia defined as a plasma glucose below 40 mg/dl, implying that values above this level are not likeky to be responsible for severe symptoms such as seizures.

Hypocalcemia:

Neonatal hypocalcemia is defined as total serum calcium level <7.5mg/dL in preterm and <8 mg/dL in term infants. The exact level of hypocalcemia at which seizure occurs is debatable. An ionized fraction of 0.6 or less may have a more predictable association with the occurrence of seizures. Hypocalcemia is divided into early onset and late onset types.

Early onset hypocalcemia:

Hypocalcemia occurring during first 3-days of life is termed early neonatal hypocalcemia. It is characteristically seen in any of 4-circumstances.

1. Prematurity
2. Severe stress or asphyxia
3. Maternal diabetes
4. IUGR

Late Neonatal Hypocalcemia:

Hypocalcemia develops after 3-5 days of life, occurs more frequently in term newborns and is not correlated with maternal diabetes, birth trauma or asphyxia. It is associated with cows' milk and formula feeding. Hyperphosphatemia is a prominent feature of late neonatal hypocalcemia. Serum calcium level frequently increase when these infants are placed on a low phosphate formula and calcium supplement. Maternal vitamin D deficiency can cause late neonatal hypocalcemia.

Hyponatremia and Hypernatremia:

Hyponatremia is a metabolic disturbance that may result from inappropriate secretion of antidiuretic hormone following severe brain trauma, infection or asphyxia but is an uncommon isolated cause of neonatal seizures. Hypernatremia also is a rare cause of seizures usually associated with congenital adrenal abnormalities from the use of IV fluids with high concentrations of sodium.

Local Anesthetic Intoxication:

Seizures are a prominent feature of neonatal intoxication with local anesthetics, inadvertently injected, usually into infants scalp, at the time of placement of paracervical, pundendel or epidural block or local anesthesia for episiotomy. Paracervical and pudendal blocks have been the most common forms of maternal analgesia involved in the well documented cases of fetal injection.

The major clinical features are characteristic and should be recognized, particularly because confusion with asphyxia is not uncommon and may delay appropriate therapy, with due consequences. Thus low Apgar score is common, in the series of seven patients reported by Hillman et al, six had scores of less than or equal to three at 1 and 5 minutes.

All infants exhibited bradycardia and hypotonia. Seizures occurred in patients within first 6 hours and were tonic in all but one. Two distinguishing features of LA intoxication aid in differential diagnosis

(1) Pupils fixed to light, and often dilated and

(2) Eye movement fixed to oculocephalic reflex.

Clinical signs suggestive of LA intoxication should alert the physician to a particularly careful inquiry in to the obstetrical history and to search for needle marks on the fetal scalp. Determination of local anesthetic levels in blood and CSF establish the diagnosis.

Other metabolic disturbances:

Inborn errors of metabolism:

Disturbances of amino acid or organic acid metabolism may result in neonatal seizures, virtually always in the context of other neurological features. Hyperammonemia and acidosis most commonly accompany these disturbances, although hyperammonemia may occur in other contexts as well. Transient disturbance of glycine cleavage enzyme may cause neonatal seizures, the diagnosis can be missed if CSF glycine levels are not determined.

Pyridoxine Dependency:

This is an autosomal recessive disorder, the seizures are caused by defective binding of pyridoxine to its apo-enzyme, which leads to reduced seizures threshold. The typical natural history is seizures beginning within hours of birth, which are difficult to control with anticonvulsant drugs but turn-off within minutes of parenteral pyridoxine. Pyridoxine in pharmacological doses control seizures, but usually recur within days of stopping pyridoxine.

The average age of onset is 4 hours but varies from birth to 3 months of age. Seizures are generalized or focal becoming generalized. The interval between giving IV pyridoxine and normalization of EEG varies from minutes to several weeks. The minimum daily requirement of pyridoxine is 2-200 mg.

A neonate with intractable seizures should be given a trial of IV pyridoxine 100 mg and should be followed. Early onset seizures responsive of pyridoxine also exists, which can successfully be treated by immediate pyridoxine repletion without the need for subsequent daily pyridoxine supplementation, this is called pyridoxine responsive seizures.

Disorder of Glucose Transport

A recently described disorder of glucose transport from blood-brain is important to recognize because prompt treatment can lead to normal neurological development. Here there is low CSF sugar with normal blood glucose concentration. The impaired glucose transport was related to a defect of the glucose transporter responsible for the facilitative diffusion of glucose across the neuronal plasma membrane.

Treatment with ketogenic diet, prevented impaired neurologic development and seizures that occurred in untreated cases.

Intracranial Infection:

Intrauterine infections or neonatal septicaemia may be associated with meningitis. About 1/3rd of patient with neonatal meningitis, present with convulsions. Intracranial infections account for 5-10% to 28% of all cases for neonatal seizures.

The most common etiologies for non-bacterial infections include toxoplasmosis, Cytomegalo virus, Herpes simplex, these infections are usually congenital, transplacentally acquired seizures usually present in the first days of life. Bacrterial infections that produce neonatal seizures include group B Streptococcus, Leisteria, E. Coli, etc. These infections usually occur towards end of first week or even later.

Early onset meningitis occurs usually during first 48 hours of life and infection appears to be derived near the time of delivery from an infected birth canal. Obstetric complications are common and infants are often LBW. Multisystemic manifestatons are common and mortality is high. Organisms causing early onset meningitis include E. coli, Leisteria and group B Streptococcus.

In late onset disease i.e., usually after 7 days of life, infection is usually acquired from infected personnel, other infants, contaminated equipment or other materials. Organisms include Staph. aureus, Pseudomons, etc. Meningitis is more common in premature than in full-term infants.

Predisposing factors related to pregnancy and delivery:

- Complications of labour and delivery
- Maternal peripartum infection
- PROM
- Chorioamnionitis

Related to Neonatal Environment:

- IV dwelling catheters
- Exposure to nursery personnel, parents or other infants harbouring pathogenic organisms.

Seizures develop at some time in illness in nearly 75% cases of late onset meningitis, although these seizures may be predominantly subtle. The convulsive phenomenon presumably related to the cortical effects of the arachnoid inflammatory infiltration. Focal seizures occur in approximately 50% of affected infants and may be prominent. These focal episodes may be related to ischemic vascular lesion.

Developmental Defects:

Many aberrations of brain development can result in seizures, which begin a any time during neonatal period. The common denominator of virtually all of these aberration is a cerebral cortical dysgenesis related most commonly to a disturbance of neuronal migration. Thus, the most frequent disorders responsible are lissenencephaly, pachygyria and polymicrogyria.

Miscellaneous Neonatal Seizures Syndrome:

Several syndromes of neonatal seizures are associated with favourable prognosis and are of unclear etiology. These benign disorders are important to be recognized to ensure appropriate management and family counseling.

Benign Familial Neonatal Convulsions (BFNC):

The epileptic syndrome BFNC is defined by the following: Onset of frequent brief seizures on or after 2nd day of life, which disappear spontaneously within a few weeks; positive family history that features on Autosomal Dominant inheritance of neonatal seizures; exclusion of other causes of neonatal seizures; normal physical examination and subsequent neurodevelopment38. Leppert et al[39] localized the gene causing BFNC to the long arm of Chr-20.

BFNC usually presents with mixed seizures type. They include all the types of neonatal seizures except myoclonic jerks and start typically with tonic, autonomic or oculofacial features. The EEG is typical in BFNC. Interictal EEG is normal. Neurocognitive development is normal in majority of the affected individuals. The risk for subsequent epilepsy is 16%. Most of the epilepsy that comes after BFNC is generalized tonic or tonic clonic with variable age at onset and duration.

Benign Idiopathic Neonatal Convulsions:

Benign idiopathic neonatal convulsions or fifth day fits describe multifocal clonic seizures, the peak time of onset of which is the fifth day, generally ceasing within 15 days. The cause is unknown, although low CSF zinc concentrations have been described in some cases. Very few cases have been reported recently. The term fifth day fits probably represents a meaningless diagnosis and should be avoided.

Othahara's Syndrome:

In Othahara syndrome, the seizures consists of brief, repetitive "tonic spasm" that can be difficult to distinguish clinically from infantile spasm. The interictal EEG shows a persistent burst suppression pattern. The etiologies for Othahara's syndrome are usually malformations of cortical development. The prognosis is poor for cognitive and motor development Successful treatment of this condition is very difficult but ACTH, prednisone, valproate and felbamate have been tried. In the Othahara's series, one third of the patients died in infancy.

Others: Some of the rare causes for neonatal seizures are:

- Benign neonatal sleep myoclonus
- Benign myoclonus of early infancy
- Early myoclonic encephalopathy.

Unknown Cause: A few cases of neonatal seizures are of unknown cause. The proportion of such case will vary inversely with the diligence of the diagnostic evaluation. Approximately 5% of cases cannot be assigned a definitive or highly probable etiology according to Volpe JJ.

DIAGNOSIS OF NEONATAL SEIZURES:

Appropriate diagnostic procedures in the newborn with seizures can be summarized from the discussion of etiologies. However, it should be emphasized that the diagnostic evaluation is often made, unnecessarily and that many diagnoses can be established nearly conclusively by such uncomplicated manoeuvres as obtaining a complete prenatal and natal history and completing a careful physical examination.

The first lab tests to be performed are directed against the two diseases that are especially dangerous but readily treated when recognized promptly i.e., hypoglycemia and bacterial meningitis. Thus LP and blood glucose (dextrostix) determination are performed urgently. Hypoglycemia is diagnosed if serum glucose level is less than 40mg/dl. In CSF analysis meningitis is diagnosed if there is increased white cells, increased protein and decreased sugar. Meningitis is confirmed by culture and sensitivity of CSF. In addition blood should be drawn also for determination of sodium, potassium, calcium, phosphorus and magnesium levels.

Other metabolic determinations and radiological and other studies are indicated the specific clinical features. Additionally focal seizures should lead to sonography of cranium and CT scan because of focal ischemic cerebral lesions. MRI and PET are done rarely and if specifically indicated. Metabolic screening is done if any metabolic disease is suspected or if there is family history of the same, eg serum ammonia for hyperammonemia.

EEG:

EEG is usually obtained in the inter-ictal period. Tracings during suspected seizures provide useful information regarding the presence of true epileptic phenomenon, but there is good evidence that epileptic discharges that are not detectable by surface EEG can occur[43]. More importantly diagnostic and particularly therapeutic manoeuvres should not be deferred for the purpose of obtaining an ictal EEG. The major values of EEG in the evaluation of neonatal seizures are:

1. To help determine whether the infant with subtle clinical phenomenon is experiencing epileptic seizures.
2. To determine whether the paralyzed infant is experiencing convulsive phenomena.
3. To define the inter-ictal background features, which are of value in estimating prognosis.

Delineation of seizure phenomena by EEG requires awareness of the normal development of EEG features in the newborn, skilled technicians and experienced readers of the EEG tracings44.

Major EEG Correlates of Neonatal Seizures:

Several points about electrical seizure activity in the newborn should be recognized. First electrical seizures are not accompanied by clinical seizures phenomena. Second, neonatal seizures tend to be brief, usually lasting less than 2 minutes. Third neonatal electrical seizures tend to be local and well localized, arising most commonly from temporal and central regions[45].

The major EEG correlates of neonatal seizures consists of focal or multifocal spikes or sharp waves or both and focal mono rhythmic discharges, occurring as a distinct change from background[46].

Ultrasonography:

First reports of real-time ultrasound images of the neonatal brain were developed in late 1970s .Real-time ultrasound scanners have become common place in most neonatal centers now.

Hypoxic ischemic cerebral injury may be recognized as increased echo density. But it is difficult to distinguish from hemorrhagic injury. In prematures USG is the method of choice for the diagnosis of PVH and PVL. Serial ultrasound scans may demonstrate characteristic sequence of increased periventricular echo density during first days of life, while subsequently resolves and becomes cystic after several weeks. 33% of small IVH will be followed by ventricular dilatation and 95% of large IVH47.

CT scan:

CT scan is done for diagnosis of intracranial hemorrhage. CT scans taken during later infancy in infants born prematurely may demonstrate features diagnostic of cerebral injury, such as PVL. The CT scan is of greater value in the term newborn than in the premature newborn for the assessment of hypoxic ischemic cerebral injury. Optimal timing of CT scan for demonstration of parenchymal hypodensities following severe perinatal hypoxic ischemia insult is between 2-4 days of life. Scan performed in later infancy may demonstrate generalized atrophy or multicystic encephalomalacia in severe cases.

Several specific patterns of hypoxic cerebral injury have been identified on CT, including the appearance of parasagittal injury, focal ischemic lesions and bithalamic and striatal hemorrhage lesions in asphyxiated term infants. The demonstration of decreased attenuation in basal ganglia on CT scan at 2 weeks of age progressing to a disproportionate dilatation of the third ventricle by 1 month of age may be a useful diagnostic feature of hypoxic ischemia injury that is localized to thalamus and basal ganglia48.

MRI:

Experience with MRI in demonstrating different neuropathology in the newborn is limited but MRI seems to be more sensitive than CT for the detection of subtle brain injuries. Recent MRI reports have suggested various patterns and timing of brain lesions in infants with HIE. MRI with its high sensitivity and anatomic resolution contributes important additional information about the time of occurrence and nature of the neuropathology underlying seizure activity. Mortality and neurological morbidity remain a major risk in term infants with neonatal seizures. MRI yields significant predictive information, which is critical to prognosis. Neonates with seizures and normal MRI have a good short-term prognosis, are less neurologically compromised and generally have a normal EEG[49].

PET:

PET is not a routine diagnostic technique. It has provided important information concerning patterns of hypoxic ischemic brain injury in both term and preterm infants.

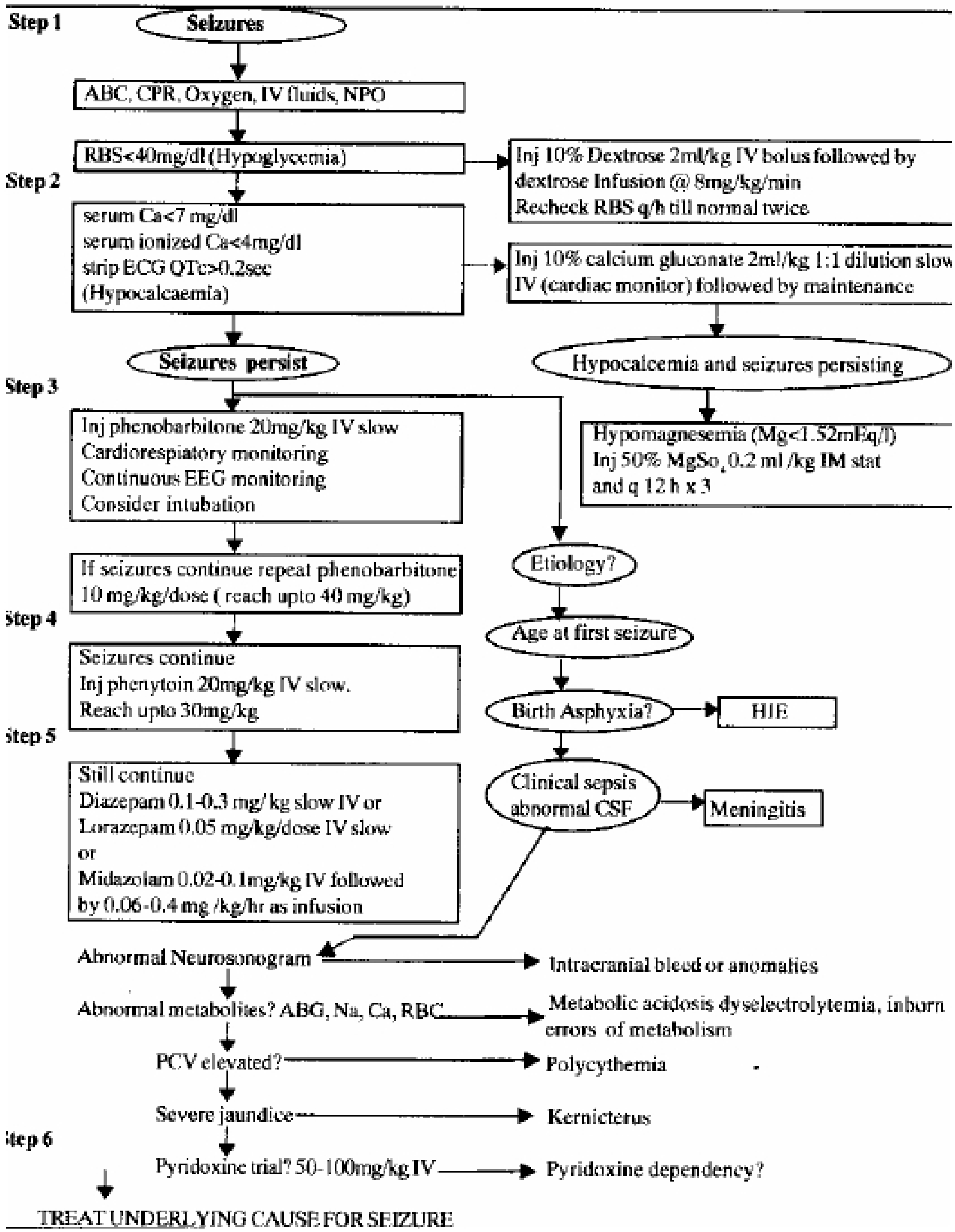
Treatment

Two principles exist. The first is to detect and treat the underlying cause of the seizure, paying particular attention to associated acute metabolic disturbances such as hypoglycemia. The second principle is the assessment of the need to control seizures, which involves balancing, the benefits of stopping some or all of the seizures against only potential deleterious effects of anticonvulsant medication.

Steps in the Management of Neonatal Seizures:

Initial steps in the management consists of stabilization of vital functions, exclusion or treatment of rapidly correctable conditions and establishing the diagnosis of neonatal seizures by clinical or EEG criteria. Specific therapies against other treatable conditions should commence but should not delay the initiation of anticonvulsant therapy. Comprehensive approach in managing neonatal seizures is shown below

Management of Neonatal Seizures



Hypoglycemia:

It is treated giving 10% Dextrose – 2 ml/Kg bolus and then continuous drip 6-8 mg/Kg / min with serial glucose measurements and then tapered down when 2 measurements are normal. If not controlled, infusion rate can be raised up to 10 mg/Kg/ min[51].

Hypocalcemia and Hypomagnesemia:

Hypocalcemia is treated by giving IV 10%. Calcium gluconate at a dose of 2ml/Kg with 1:1 dilution slowly over 15-20 minutes with cardiac monitoring and if seizures continue, hypomagnesemia should be suspected and Inj. MgSO4 50% at dose of 0.2 ml/Kg IM is given BD for 3 days.

Seizure Control:

Prolonged and poorly controlled neonatal seizures have been associated with worse outcome than infrequent or readily controlled seizures, but severity of the underlying disorders may account for both poor seizure control and adverse outcome. Many of the commonly used anticonvulsant regimens are ineffective in controlling all seizures clinically or electrically. It is probably wise to attempt to control frequent or prolonged seizures, particularly if causing disturbance of ventilation and blood pressure. After clinical seizure control, persisting EEG seizures are rarely treated, as they tend to be brief and fragmentary, further treatment increase the risk for side effects.

Anticonvulsants

Phenobarbitone:

Phenobarbitone continues to be the first line drug for the treatment of neonatal seizures. An initial IV loading dose of 20 mg/Kg achieves clinical control in 40% of neonatal seizures, increasing to 70% when further 10 mg/Kg doses are administered to a final loading dose of 40 mg/Kg. The therapeutic range is generally considered to 20-40 μg/ml. The maintenance dose is 3-6 mg/Kg/day, given 12 hourly in divided dose. Control is more likely to be achieved in babies without status epilepticus and with mild to moderate EEG abnormalities.

Phenytoin:

Phenytoin is used as a second line drug when neonatal seizures are not controlled by phenobarbitone alone. A loading dose of 20 mg/Kg is given IV at a rate not greater than 1 mg/kg/min with cardiac monitoring.

Benzodiazepines:

Most of the benzodiazepines have been tried in newborn. Diazepam has a very long half-life in babies, of approximately 30-75 hours, and because of the respiratory depressant effects that occur when levels accumulate this is not suitable for prolonged infusions. Midazolam can be used, if not responding above mentioned drugs at a dose of 0.01 to 0.03 mg/Kg and infusion.

Other Drugs:

Sodium valproate may be effective because it acts on GABA receptors, but it has potential for liver toxicity. Vigabatrin is not available in an IV form.

Duration of Therapy: Duration of therapy depends on:

1. The neonatal neurological examination.
2. The cause of neonatal seizures.
3. The EEG.

These three factors should be assessed carefully in each newborn wit seizures to determine duration of therapy. If neurologic examination persistently abnormal, etiology is considered and EEG is obtained. In general baby is assessed at 1 month of age and if neurological examination is normal, phenobarbital is discontinued over 2 weeks, if it is not normal, an EEG is obtained, if the study is not overtly paroxysmal, phenobarbital is tapered. If EEG is overtly paroxysmal, phenobarbital is continued and reassessed at 3 months of age52.

Other modes of therapy:

Seizures related to other metabolic disturbances are treated accordingly. Meningitis is treated with intravenous antibiotics according to sensitivity and organism cultured for 2-3 weeks period. Specific therapy sometimes must be supplemented with administration of anticonvulsants at least during neonatal period.

Reemphasis should be made of recurrent seizures that are not accompanied by any abnormal associated finding to aid in diagnosis. This situation should raise the possibility of pyridoxine dependency. The best means of diagnosis is the therapeutic trial of pyridoxine, administered IV in a dose of 50-100 mg, accompanied by simultaneous monitoring of EEG. In the true case this trial is accompanied by cessation of seizures within minutes and normalization of EEG within minutes or hours.

Other disorders like hyponatremia, hypernatremia, inborn errors of metabolism should be treated accordingly. Finally, it is becoming increasingly clear that some infants with neonatal seizures recalcitrant to therapy, particularly seizures related to developmental disturbances of brain e.g., hemimegelencephaly, ultimately will benefit from surgical therapy53. Although usually carried out later in infancy, with improvement in cerebral electrophysiological monitoring and in surgical technique, earlier interventions may be warranted.

Prognosis:

The prognosis for infants with neonatal seizures has improved over last decades. These improvement relate in large part to improved obstetrical management and modern neonatal care. The incidence of neurological sequelae in surviving changed much less.

Overall outcome of infants with neonatal seizures varies considerably as a function of gestational age. Clearly outcome is poor among the smallest infants, who have most serious life threatening illness[54].

Relation to EEG:

The inter-ictal EEG is of value in establishing prognosis of neonatal seizures. The background EEG was found to correlate especially well with the outcome

Table-4: Relationship of EEG background with Neurological Sequelae

EEG background	Neurological sequelae
MILD ABNORMALITY	LESS THAN 10%
MODERATE ABNORMALITY	50%
SEVERE ABNORMALITY	90%

Relation to the Neurological Disease:

The most important determinant of neurological prognosis is the nature of the neuro-pathological process that underlies the seizures. Nearly all data are based on periods of follow-up that do not extend in the school age, thus, the incidence of subtle but potentially important intellectual deficits is largely unknown[57 58].

Table-5: Relationship of Neurological Disease with Development

Neurological disease	Normal development
HIE	50%
IVH	10%
SAH	90%
Hypocalcemia	50%
Early onset	100%
Late onset	
Hypoglycemia	50%
Bacterial meningitis	50%

These data indicate that the major task of physician is to determine as precisely as possible the neurological disease producing the seizures. The task is not only to dignose the etilogy of neonatal seizures but also institution of appropriate treatment and explain the outcome.

MATERIALS AND METHOD

Methods of Collection of Data:

The present study included 102 neonates presenting with seizures admitted to NICU of Raja Mirasdhar Govt. Hospital, Thanjavur Medical College, Thanjavur, during the period of eight months from January 2014 to August 2014.

Inclusion Criteria:

Neonates (first 28 days of life) presenting with at least one of the following clinical type of seizures:

- Generalized tonic seizures.
- Multifocal clonic seizures
- Focal clonic seizures
- Myoclonic seizures
- Subtle activity with apnea or autonomic features.

Exclusion Criteria:

- Seizure like activity (jitteriness, tetanic spasm, etc.) instituted, but also to ensure as meaningful a prognostic statement as possible
- Subtle activity without apnea or autonomic features

Detailed antenatal, natal and post natal history were taken as per the proforma enclosed.

Antenatal History:

Age & parity of mother were noted. History of whether regular antenatal check-ups were done or not was enquired. History of medical illness like diabetes, fever during first trimester or third trimester were asked. History of obstetric complications like PIH, eclampsia, antepartum hemorrhage, oligo or polyhydramnios were taken.

Perinatal History:

History of PROM, prolonged second stage of labour, Meconium staining of liquor, place of delivery, type of delivery and indication for forceps and caesarean section, were enquired. After delivery whether baby cried immediately or not, was it meconium stained and any resuscitation done, were enquired. If Apgar score was done, it was noted. The neonate was diagnosed with birth asphyxia if baby did not cry for more than three minutes after birth or documented Apgar score was ≤ 3 at one minute and < 7 at 5 minutes of birth.

Post-natal History:

History of lethargy, poor feeding, jaundice, excessive cry, fever, vomiting and seizures were taken.

History of Seizures:

The day of onset of seizures, type of seizures, the duration of seizures, number of seizures and consciousness during and between seizures were taken.

After appropriate history, detailed examination of neonate was done.

Examination:

The vitals of the baby (Heart Rate, Respiratory Rate, Peripheral pulses, Blood pressure, temperature, and Capillary filling time) were recorded. General physical examination of neonate was done according to the proforma and any disparity in Head size and Shape, Skin lesions were noted. Anthropometry of the neonate was recorded & gestational age was assessed according to New Ballard scoring. CNS examination was done as per the proforma and HIE was staged according to modified Sarnat's staging in to stage I, II and III. Other systems were also examined.

The following investigations were done for neonatal seizures:

- Complete blood count (haemoglobin, Total count, differential count).
- Sepsis screening: Peripheral smear for band cells and toxic granules, CRP and blood culture if necessary.
- Blood glucose: Random blood sugar was done urgently with glucostick and then confirmed by glucose oxidase method. Hypoglycemia was diagnosed if RBS is less than 40 mg / dL.
- Serum electrolytes: Serum electrolytes were done on emergency basis, serum calcium, sodium and potassium were done. Hypocalcemia was

diagnosed if serum calcium level was less than 8.0 mg/dL. Hyponatremia was diagnosed if serum sodium level is less than 130 mEq/L and hypernatremia if serum sodium is >150 mEq/L.

- CSF analysis: If septicemia or meningitis was suspected, LP was done and CSF analysed for colour, turbidity, protein, sugar, total and differential cell count and culture. Neonatal meningitis was diagnosed if CSF culture showed growth of organisms.

Other metabolic screening like serum ammonia was done if particular metabolic disease was suspected.

Radiological investigations:

Chest x-ray was done to rule out meconium aspiration syndrome and respiratory distress syndrome

Ultrasound of cranium: was done in all babies with neonatal seizures to rule out intracranial hemorrhage, hydrocephalus, congenital anomalies of brain and infarction.

CT scan of Head: CT scan of head was done as & when necessary.

All the patients were treated according to the diagnosis.

RESULTS

Analysis of Cases and Results:

There were 102 neonates admitted to RMH, THANJAVUR MEDICAL COLLEGE, THANJAVUR, with convulsions during the period of 8 months from January 2014 to August 2014

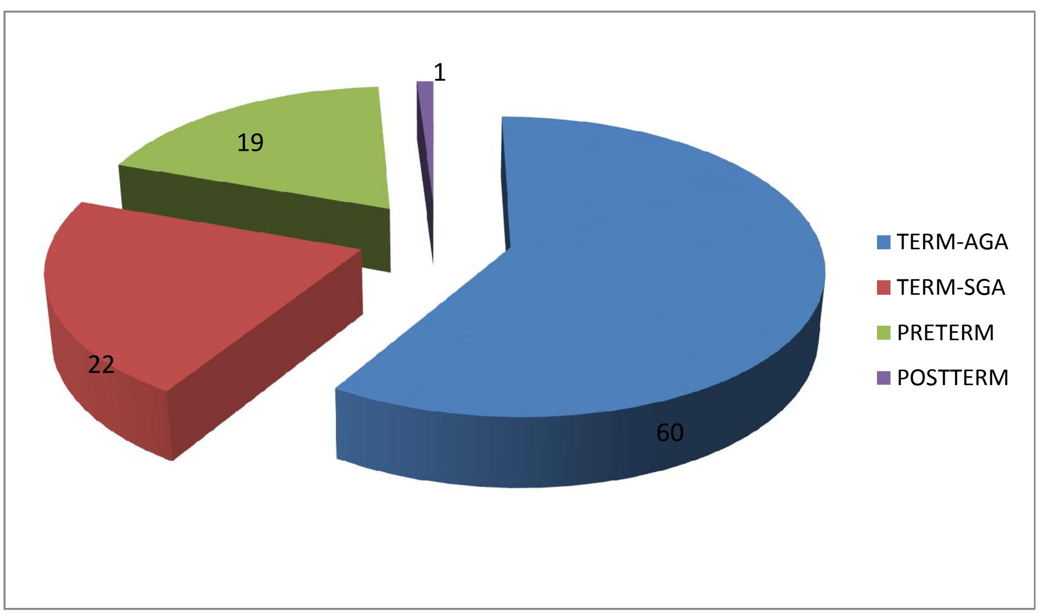
Gestational Age:

Table-6: Distribution of Neonatal Seizures according to gestational age

Gestational age	No. of Cases	Percentage
Term – Appropriate for gestational age (AGA)	60	58.82
Term – small for gestational age (SGA)	22	21.60
Preterm	19	18.60
Post-term	1	0.98
Total	102	**100.00**

In the present study, out of 102 babies, 82 were full term. Among these 82 full term neonates 60 (58.82%) were appropriate for gestational age and 22 (21.6% were small for gestational age. There were 19 (18.6%) preterm babies and 1 post term baby).

Figure-1: Distribution of Neonatal Seizures according to gestational age

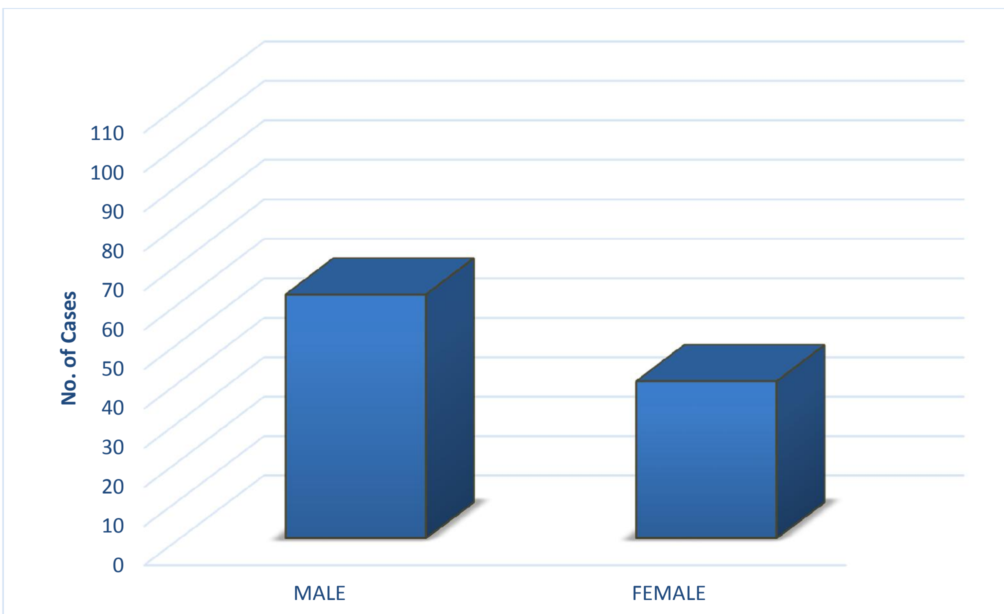


. **Table-7: Sex wise distribution of neonatal seizures**

Sex	No. of Cases	Percentage
Male	62	60.80
Female	40	39.20
Total	102	**100.00**

In our study, 62 were males and 40 were female babies with male to female ratio of 1.5:1.

Figure-2: Sex wise distribution of neonatal seizures



Place of Delivery:

Table-8: Place of Delivery of babies with neonatal seizures

Place of Delivery	No. of Cases	Percentage
Home delivery	13	12.75
Hospital delivery	89	87.25
Total	102	**100.00**

Out of 102 cases, 13(12.75%) were born at home and 89 (87.25%) at hospital. Out of hospital deliveries 70 were inborn and 19 were out born.

Figure-3: Place of Delivery of babies with neonatal seizures

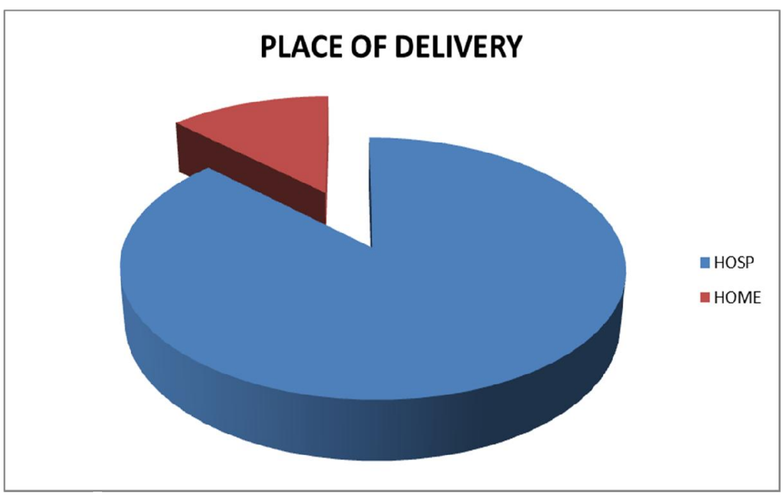
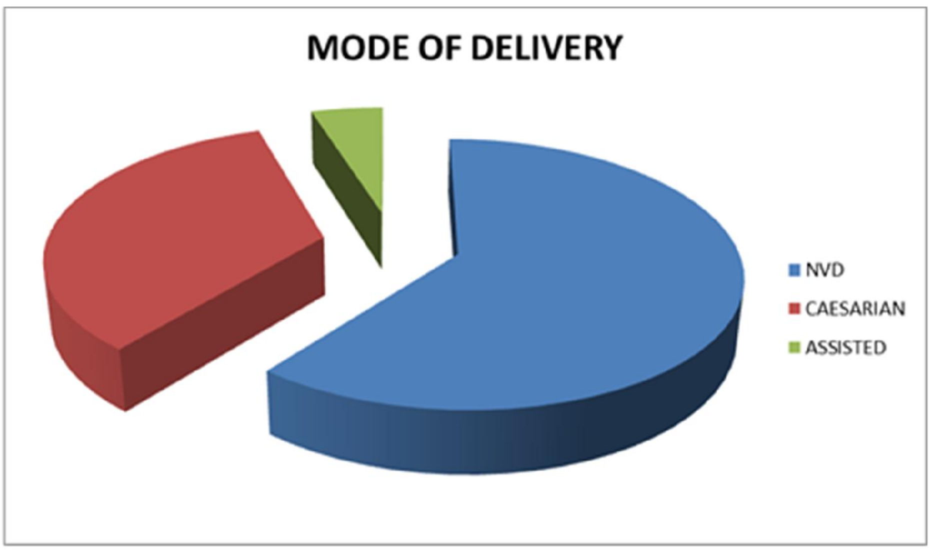


Table-9: Type of Delivery of babies with neonatal seizures

Type of Delivery	No. of Cases	Percentage
Spontaneous vaginal delivery	62	60.80
Caesarian section	35	34.30
Outlet forceps delivery	5	4.9
Total	102	**100.00**

FIGURE 4: Type of Delivery of babies with neonatal seizures:



Majority of the neonates in the present study were born by spontaneous vaginal delivery in 62 (60.8%) cases. Caesarean section was done in 35 cases (34.3%) the indications were prolonged second stage of labor with MSAF in 12 cases PIH in 4 cases. Forceps delivery were done in 5 cases (4.9%) and the indication was prolonged second stage of labour in 4 cases.

Antenatal Details:

In the present study 8 babies were born to mothers with PROM, 8 babies were born to mothers with PIH, 2 babies were born to mothers with APH and two and one mother had fever during first and last trimester respectively.

Natal Factors:

In our study 72 mothers had prolonged 2nd stage of labor (>2 hours), out of which 42 had birth asphyxia. 29 mothers had meconium stained amniotic fluid, out of which 20 had birth asphyxia.

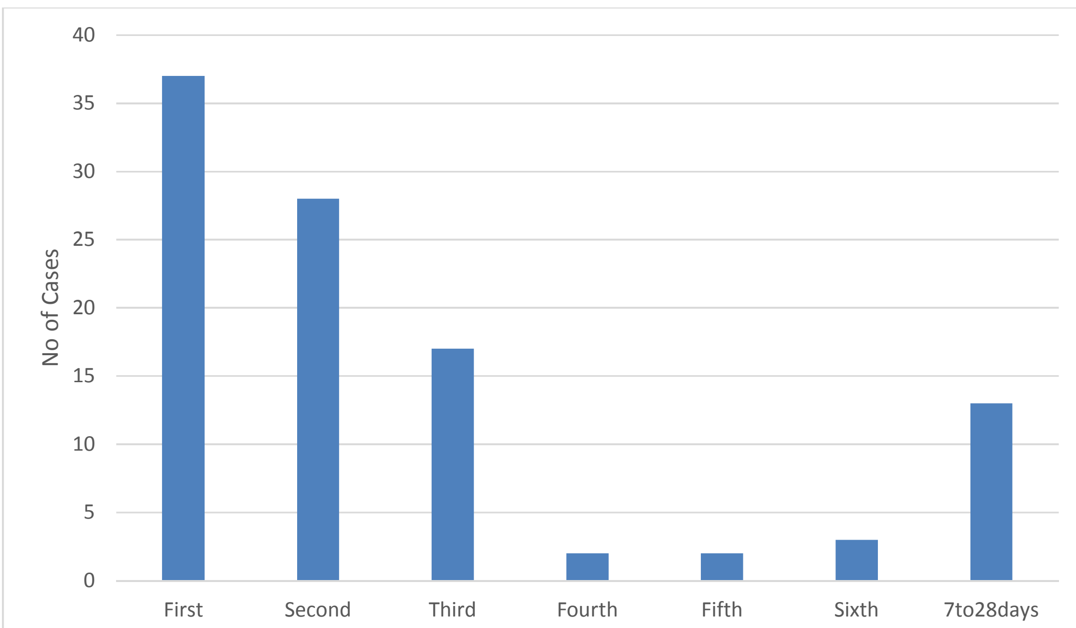
Day of onset of Neonatal Seizures

Table-10: Day of onset of Neonatal Seizures

Days of onset of Neonatal Seizures	No. of Cases	Percent
First	37	36.27
Second	28	27.45
Third	17	16.67
Fourth	2	1.96
Fifth	2	1.96
Sixth	3	2.94
7to28days	13	12.75
Total	102	**100.00**

In our study onset of seizures on first day of life was seen 37 neonates (36.27%), on second day of life 28 neonates developed seizures (27.45%), on third day of life 17 (16.67%) babies developed convulsions. The first three days of life together constituted 80.39% of neonatal seizures.

Figure-5: Day of onset of Neonatal Seizures



Type of Neonatal Seizures

Seizures were classified according to Volpe as:

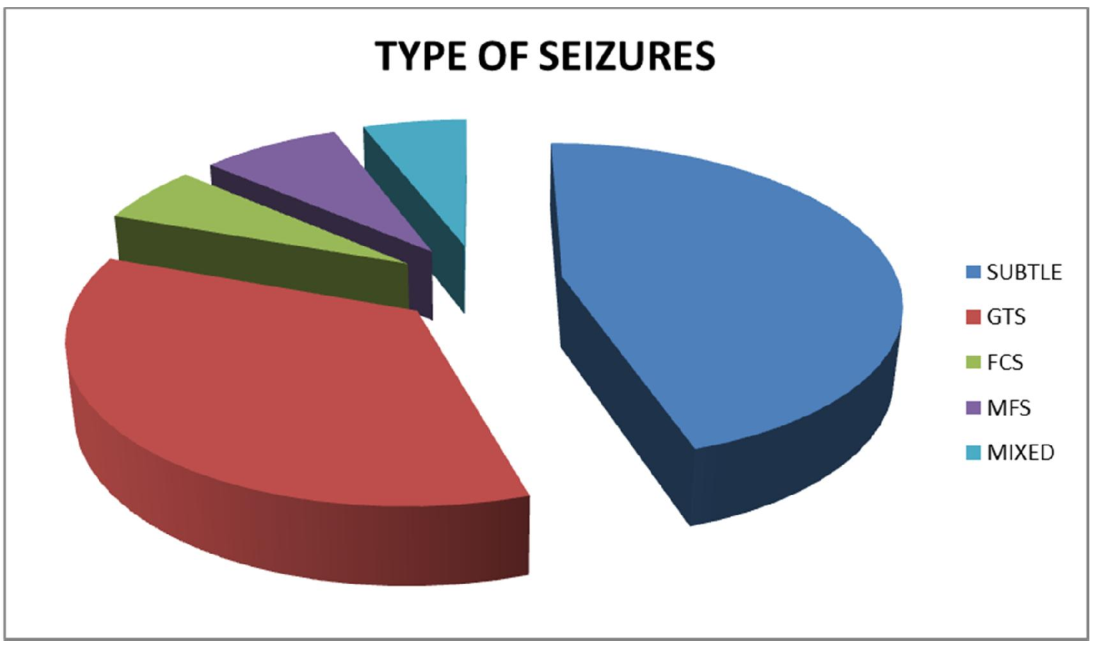
- ❖ Generalized tonic.
- ❖ Subtle
- ❖ Multifocal and focal clonic and
- ❖ Myoclonic seizures.

Table-11: Type of Neonatal Seizures

Type of Neonatal Seizures	**No. of Cases**	**Percent**
Subtle	46	45.1
Generalized tonic	36	35.4
Multifocal clonic	8	7.8
Focal clonic	6	5.9
Subtle with GTS	3	2.9
Subtle with clonic	3	2.9
Total	102	**100.00**

In our study out of 102 neonatal seizures, 96 neonates had one of the 4 classically described neonatal seizures. Among these 46 neonates (45.1%) subtle seizures, 36 neonates (35.4%) had generalized tonic seizures, 8 (7.8%) had multifocal clonic seizures and 6 (5.9%) had focal clonic seizures. 6 neonates had mixed type of seizures, among these 3 had subtle with generalized tonic seizures and 3 had subtle with clonic seizures.

Figure-6: Type of Neonatal Seizures



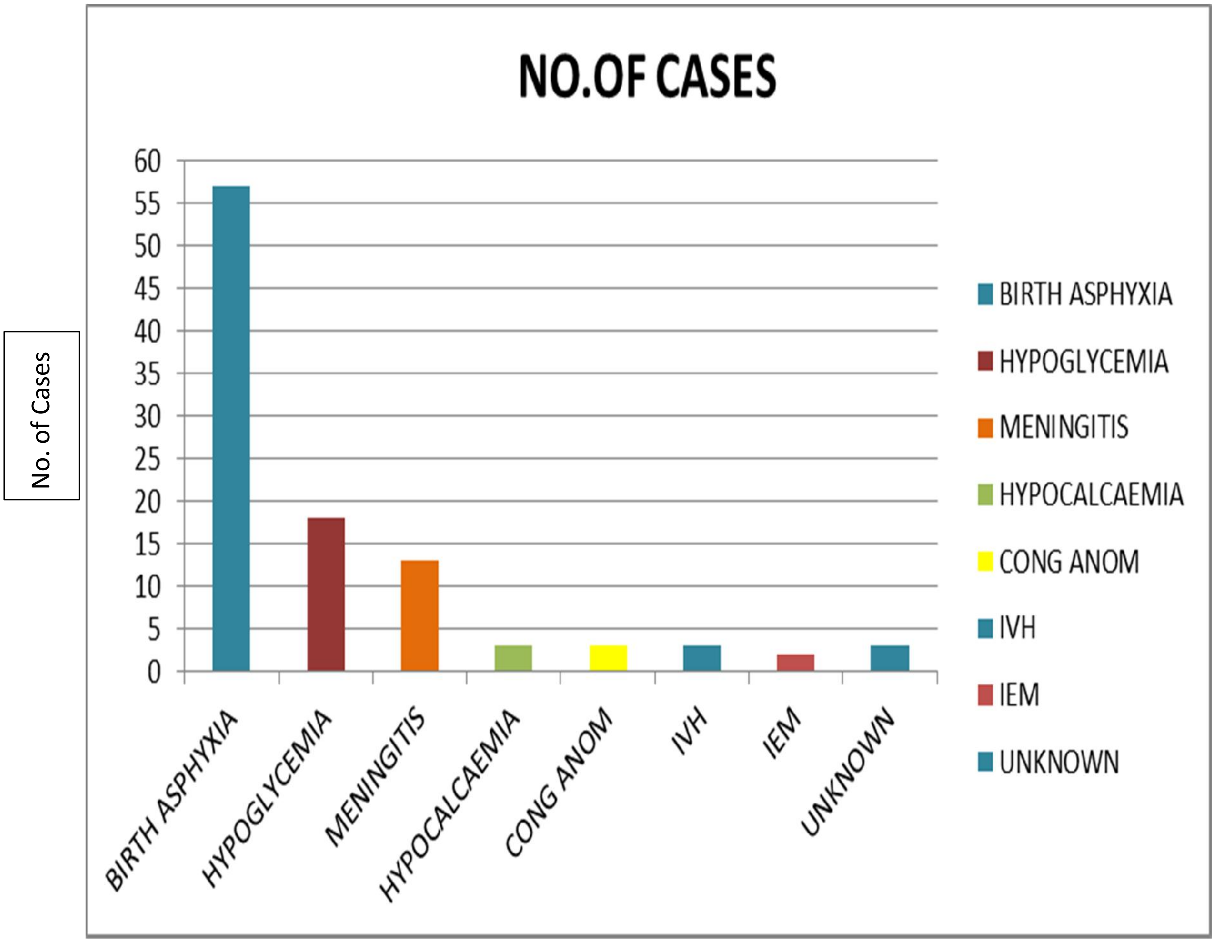
Etiology of Neonatal Seizures

Table-12: Etiology of Neonatal Seizures

Etiology	No. of Cases	Percent
Birth asphyxia	57	55.90
Hypoglycemia	18	17.64
Neonatal meningitis	13	12.74
Hypocalcemia	3	2.94
Congenital anomaly	3	2.94
Hemorrhagic disease of newborn	3	2.94
Hyperammonemia	2	1.96
Unknown	3	2.94
Total	102	**100.00**

Birth asphyxia is the commonest cause of neonatal seizures in our study. 57 babies had birth asphyxia (55.9%) and 3 babies had birth asphyxia with hypoglycaemia and 1 baby had hypocalcaemia. 18 babies had hypoglycemia (17.6%), 13 babies had meningitis (12.7%), 3 babies had hypocalcemia (2.9%). 2 baby had IEM. 3 baby had intraventricular hemorrhage (2.9%). 3 babies had congenital anomalies as a cause for neonatal seizures (2.9%). In 3 neonate, no cause was identified.

Figure-7: Etiology of Neonatal Seizures



Birth asphyxia is the commonest cause of neonatal seizures in our study

Correlation of etiology with day of onset of neonatal seizures:

Table-13: Correlation of etiology with day of onset of neonatal seizures:

Day of onset of seizure	Etiology										Total	Percent
	Birth Asphyxia		Metabolic				Neonatal Meningitis		Others			
			Hypoglycemia		Hypocalcemia							
	No.	%	No.	%	No.	%	No.	%	No.	%		
1	38	97.44	-	-	-	-	-	-	01	2.56	39	100
2	12	54.54	06	27.27	01	4.55	01	4.55	02	9.09	22	100
3	6	42.86	05	35.71	01	7.14	02	14.29	-	-	14	100
4	1	25	03	75	-	-	-	-	-	-	04	100
5	-	-	01	50	-	-	01	50	-	-	02	100
6	-	-	01	12.5	-	-	03	37.5	04	50	08	100
7-28	-	-	02	15.38	01	7.7	06	46.15	04	30.77	13	100
Total	57		18		03		13		11		102	

Chi squared for onset of seizures on first three days and more than three day with etiology =72.84 with p value of < 0.001 (statistically highly significant for onset of seizures on first three days of life with birth asphyxia). The onset of seizures on first day was seen in 39 neonates, 38 of them were due to birth asphyxia and one was due to congenital anomaly.

On 2nd day 22 babies developed seizures and 12 (54.54%) were due to birth asphyxia, 6 were due to hypoglycemia alone, 1 was due to hypocalcemia and 1 was due to meningitis and 2 were due to congenital anomaly.

FIGURE 8: Correlation of etiology with day of onset of seizures

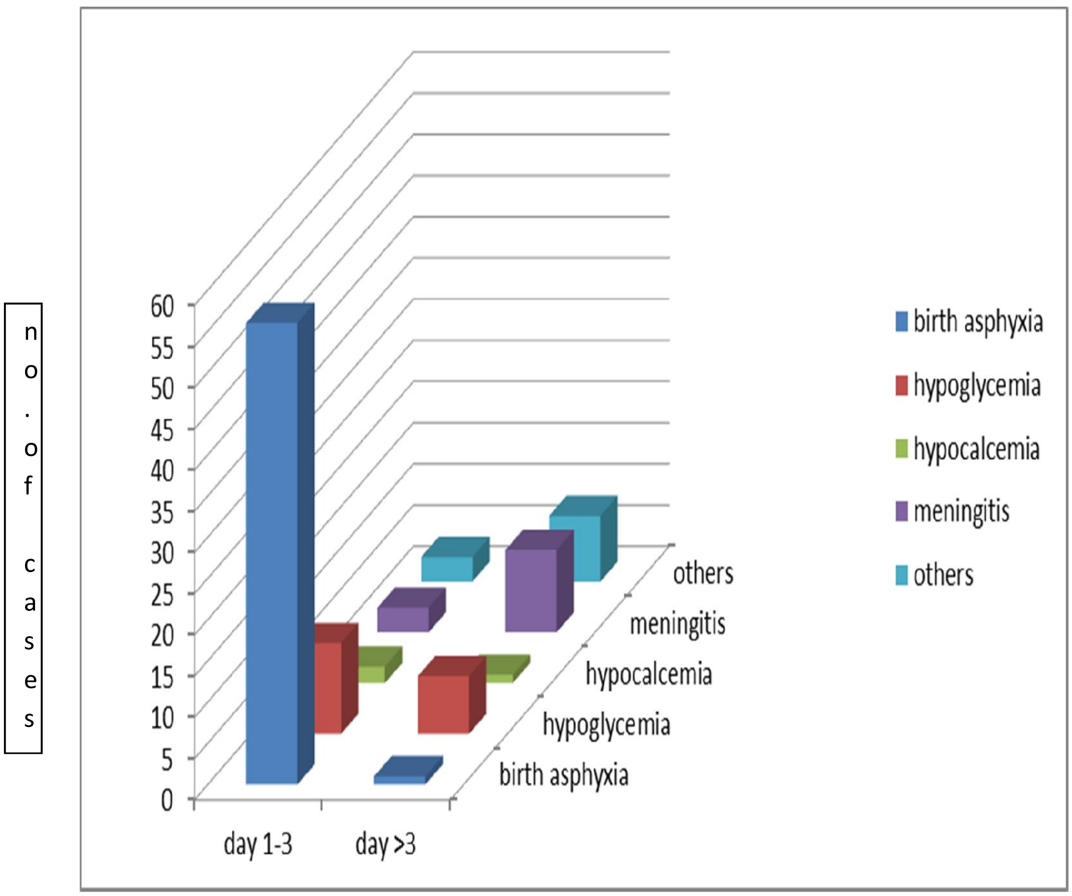


Table-14: Correlation of Etiology with type of neonatal seizures:

	Type of Seizures					Total	
	Subtle	GTS	MFC	FCS	Mixed		
	No.	No.	No.	No.	No.	No.	
Birth Asphyxia	28	19	4	4	2	57	100.00
Hypo-glycemia	8	6	1	2	1	18	100.00
Hypo-calcemia	--	2	01	--	--	3	100.00
Meningitis	6	5	1	--	1	13	100.0
Others	4	4	1	--	2	11	100.00
Total	46	36	8	6	6	102	

Chi squared for neonates with GTS, Subtle seizures and clonic seizures with etiology = 0.27 – p>0.05 not significant. In present study, out of 57 neonates with birth asphyxia, 28 had subtle seizures, followed by GTS in 19 neonates & MFC in 4 neonates. In neonates with hypoglycemic seizures, 8 babies had subtle seizures followed by GTS in 6 neonates. In neonates with meningitis (13 neonates), 6 developed subtle seizures and 5 had GTS. In our study there was no correlation between types of neonatal seizures with the etiology (p>0.05)

Figure-9: Correlation of Etiology with type of neonatal seizures

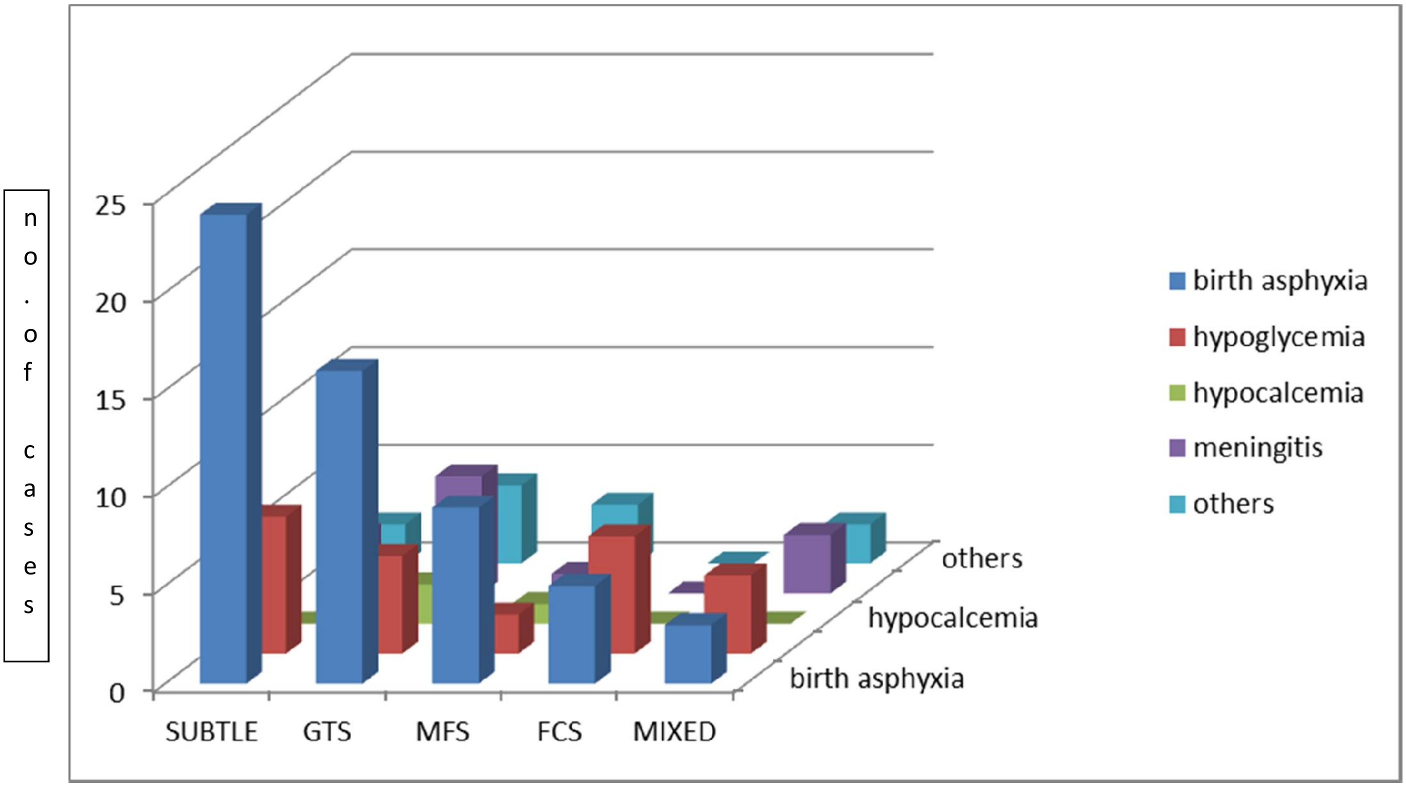


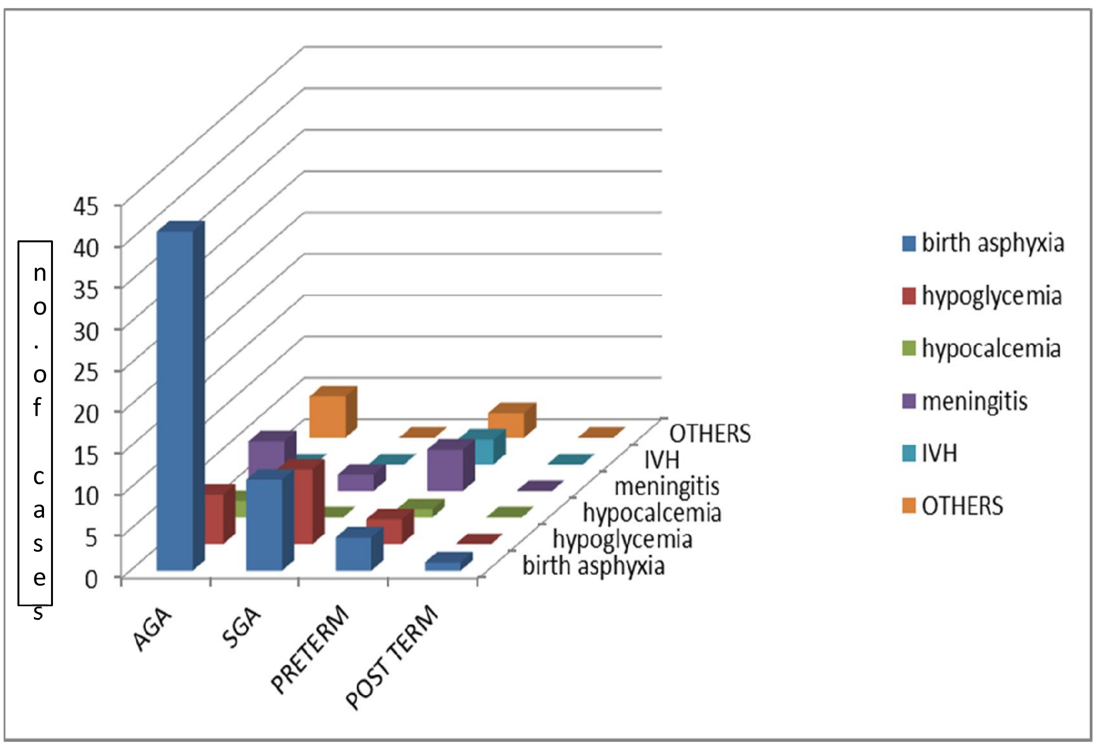
Table-15: Correlation of Etiology of Neonatal Seizures to Gestational Age

Etiology	Gestational Age								Total	
	Term				Preterm		Post-term			
	AGA		SGA		Preterm		Post-term			
	No.	%	No.	%	No.	%	No.	%	No.	%
Birth asphyxia	41	71.9	11	19.2	4	7	01	1.7	57	100.0
Hypoglycemia	6	33.3	9	50	3	16.6	--	--	18	100.0
Hypocalcemia	2	66.6	--	--	1	33.3	--	--	3	100.0
Neonatal meningitis	6	46	2	15.3	5	38.4	--	--	13	100.0
IVH	--	--	--	--	3	100	--	--	03	100.0
Others	5	62.5	--	--	3	37.5	--	--	08	100.0
Total	60		22		19		01		102	100.0

Chi squared for neonates≥2500 gm & < 2500gm with etiology.2 = 16.99, P < 0.001. In the present study, out of 60 term AGA babies, 41 had birth asphyxia, 5 had asphyxia with septicemia, 6 had hypoglycemia,6 had meningitis, 2 had hypocalcemia, 2 had congenital anomaly and hyperammonemia, hyponatremia with meningitis and unknown cause were seen in one case each. Out of 22 IUGR, term babies, 11 had birth asphyxia, 9 had hypoglycemia, one had hypoglycemia with birth asphyxia and 2 had meningitis.

Out of 19 preterm babies, 3 had hypoglycemia, 4 had asphyxia and 1 had hypocalcaemia and 5 had meningitis and 3 had IVH. Out of 1 post-term baby and had birth asphyxia. Low birth weight babies are more prone for seizures due to hypoglycemia with statistically significant P value of < 0.001.

Figure-10: Correlation of Etiology of Neonatal Seizures to Gestational Age



Birth Asphyxia:

Hypoxic ischemic encephalopathy was found to be the commonest cause of neonatal seizures in our study i.e., in 57 cases (55.8%). Isolated birth asphyxia was responsible in 53 cases (51.9%) and in remaining 3 cases, hypoglycemia was also seen (2.9) and 1 case hypocalcaemia.

Type of Delivery:

In our study among the 57 neonates with birth asphyxia 30 were born by normal vaginal delivery, among these in the antenatal history 42 (73%) had prolonged second stage of labour, 20 (35%) had MSAF and 8 neonates were delivered at home. 24 neonates were delivered by LSCS, and indication was prolonged second stage of labour with fetal distress in 14 cases (58%). 3 neonates were delivered by forceps & all mothers had prolonged second stage of labour.

Day of Onset of Convulsion in Birth Asphyxia:

In our study out of 57 cases of birth asphyxia with neonatal seizures, 38 babies developed convulsion on first day of life (66.6%), 12 babies (21%)

developed seizures on second day of life, 6 babies (10.5%) developed seizures on 3rd day and one baby developed seizures on 4th day. Majority of babies with birth asphyxia developed seizures within first 72 hours of life and more so within first 24 hours of life.

Table-16: Type of seizures in Birth Asphyxia

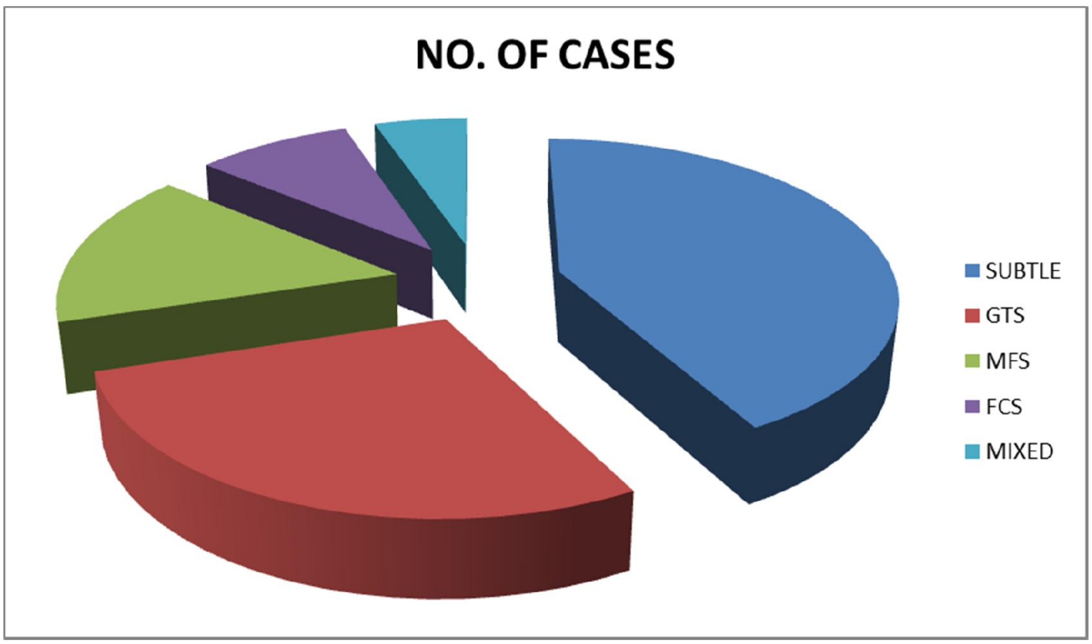
Type of convulsion	No. of Cases	Percent
Subtle	28	49%
GTS	19	33.3%
Multifocal clonic	4	7%
Focal clonic	4	7%
Mixed type	2	3.5%
Total	57	**100.00**

In the present study, out of 57 neonates with birth asphyxia, 28 neonates (49%) had subtle seizures, 19 babies (33.3%) had GTS, 4 babies (7%) had multifocal clonic seizures, and 4 babies had focal clonic seizure.

Perinatal and Antenatal factors:

In our study in neonatal seizures with birth asphyxia (57cases) 42 mothers had prolonged second stage of labour, 20 mothers (33.3%) had meconium stained liquor, 6 mothers had PROM and 5 mothers had PIH.

Figure-11: Type of seizures in Birth Asphyxia



Metabolic Disorders:

Hypoglycemia:

Hypoglycemia was the second most common cause of convulsions in neonates in our study. There were 18 babies with hypoglycemia (excluding complicated hypoglycemia associated with birth asphyxia) who presented with seizures. 6 babies with hypoglycemia had onset of seizures on 2nd day, 5 had onset on third day, 3 on fourth day and 1 each on 5th, 6th, 2 on 7 to 28 days. Majority of hypoglycemic convulsions occurred on 2nd day (33.3%) followed by 3rd (27.75%)

Out of 18 babies, 9 were small for gestational age babies (50%), 6 were term AGA babies and 3 were preterm babies.

Hypocalcemia:

In present study there were 3 babies with hypocalcemia who presented with seizures. One baby presented on second day with seizures i.e., early onset hypocalcemia. One presented in third day and the other during 4th week (late onset hypocalcemia).

Others:

In our study one baby had hyponatremia with neonatal meningitis, presented during 2nd week of life. Two babies had hyperammonemia, presented during 2nd week.

Neonatal Meningitis:

13 babies were diagnosed as neonatal meningitis in our study and was the third most common cause of neonatal seizures. One case had hyponatremia with neonatal meningitis. Two neonates presented with seizures on 3rd day, 4 neonate presented between 4th to 7th days and remaining 6 neonate presented between 2nd to 4th week of life.

In babies with meningitis 6 babies had generalized tonic seizures, 3 had subtle seizure, one had multifocal clonic seizures and 3 had mixed seizures.

Out of 13 babies with neonatal meningitis, 3 were born at home and 1 mother of a baby had fever before and during delivery. Out of 13 babies with Neonatal meningitis, 2 were IUGR babies.

Intracranial hemorrhage:

In the present study only 3 preterm babies of 32 weeks of gestation developed convulsions, diagnosed by ultrasound of cranium.

Congenital anomalies:

A female baby presented on 1 day with subtle seizures had hydrocephalus presenting with macrocephaly and protruded eyes. A male baby presented with convulsions (multifocal clonic type) on 2nd day. The baby had prominent frontal and parietal eminence with short unequal limbs, simian crease and microcephaly. A case with meningomyelocele presented with subtle seizure on 6th day of life. The diagnosis was not known in a patient presenting with seizures (GTS) All the investigations were within normal limits.

Mortality:

Mortality in our study was 17.6% (18 cases) and birth asphyxia was the commonest cause seen in 10 cases (55.5%).

DISCUSSION

In the present study 102 neonates with seizures were studied in 6 months period. Both intramurally and extramurally delivered babies were included in the study.

Neonatal seizures in relation with gestational age:

In our study, out of 102 neonates with seizures 83 were full-term neonates (81.3%), of which 60 were appropriate for gestational age i.e., B.Wt. ≥2500 gm (58.8%) and 22 were small for gestational age i.e., <2500 gm (21.6%). 19were preterm babies (18.6%) and 1 was post term babies.

Majority of neonates with seizures in our study were full term babies. Birth asphyxia was the commonest cause of seizures in full term babies and is associated with perinatal complications like prolonged second stage of labour seen in 42 cases, MSAF in 20 cases.

Similar observations was seen in study by Ravneet Sandhu et al[59] where term AGA babies were 81.2% followed by preterm babies in 18.8%. Small for gestational age babies constitute significantly for neonatal seizure cases. In our study 21.6% were SGA babies, similar observation was seen in study of neonatal seizures by Sahiba Rima M et al[60], where SGA babies were 24 (20%) out of 122 term babies, which is similar to our study.

Sex Distribution:

Neonatal seizures has no sex predilection. However, in our study, male to female ratio was 1.5:1, similar with the study of neonatal seizures by Lakra Mahaveer[13] et al where male to female ratio was 2:1.

Type of Delivery:

In our study majority of neonates with seizures were born by normal vaginal delivery (60.8%) followed by LSCS (34.3%) and outlet forceps delivery (4.9%). In a study of neonatal seizures by Lakhra Mahaveer et al[61] [68].7% were born by normal vaginal delivery, 28.1% by LSCS and 3.1% by forceps delivery.

Perinatal Factors:

In the present study, majority of babies with birth asphyxia had prolonged second stage of labour i.e., 42 of 57 (73.6%) and difficult delivery, 20 cases and MSAF (35.0%) and 5 mothers had PIH. Myles TD etal[62] found slightly higher incidence of birth asphyxia with prolonged second stage of labour compared to normal second stage of labour.

Day of Onset of Seizures:

In our study 82 out of 102 neonates with seizures had onset within first three days of life, among these 63% had onset of seizures within first 2 days life and 36.3% had onset of seizures within first day of life. 20 neonates (19.5%) had onset of seizures after 3 days of life, In a study of neonatal seizures by Ronen Gabriel et al[63] onset of seizures on first day of life was 36%, 64% had onset of seizures within first 48 hours, and 83% within first week of life, which is similar to our study.

Onset of seizures within first 3 days constitute the majority of cases, more so within first 48 hours of life. After 3 days there is a small second peak at the end of first week and early second week.

Type of Neonatal Seizures:

In the present study 46 (45%) babies had sutble seizures either in the form of oro-buccal movements, eye blinking, cycling movements of limbs or apnea associated with tachycardia (i.e., HR > 160/min) or hypertension. Generalized tonic seizures was observed in 35.4% i.e., 36 cases followed by multifocal clonic in 8 cases (15%), focal clonic seizures in 6 babies (5.88%) and 6 babies had mixed type of seizures. In a study of neonatal seizures by Brunquell Philip J et al[12] sutble seizures were the commonest occurring in 51% (27 of 53), followed by focal clonic (42%), multifocal clonic (30%) and GTS (23%). Lakra Mahaveer et al[13] also reported that subtle seizures were the commonest. But in a study of neonatal seizures by Soni Arun et al[64] generalized tonic seizure was commonest type of seizure, followed by subtle seizures.

In contrary to older children and adults, neonates present with subtle and generalized tonic seizures more commonly because of immaturity of central nervous system and more mature limbic system compared to other parts of CNS in neonates.

Subtle seizures are difficult to recognize and also difficult to interpret, as they may be normal neonatal activity and one should be careful in assigning subtle movements as seizures in neonates.

Etiology of neonatal seizures:

Birth asphyxia is the most common cause of neonatal seizures in our study (57 of 102 cases – 55.8%) followed by metabolic seizures in which hypoglycemia was the commonest in 18 babies (17.6%), 3 babies had hypocalcemia. Neonatal meningitis was seen in 13 babies (12.7%). Congenital anomaly and hyperammonemia were seen in 3 babies each. Birth asphyxia is the commonest cause of neonatal seizures in studies by Soni Arun et al[64] seen in 76.9% of cases and Ronen Gabriel et al[63] seen in 40% of cases.

Table-17: Comparison of Etiology of Neonatal Seizures:

Study group	HIE		Metabolic		Infection		ICH		Others		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Present study	57	55.8	21	20.5	13	12.7	3	2.9	8	7.8	102	100
Ronen Gabriel et al[63]	36	40.0	17	19.0	18	20.0	10	11.0	9	10.0	90	100
Lakhra Mahaveer et al[61]	21	33.0	19	30.0	18	28.0	3	5.0	3	4	64	100
Sandhu Ravneet et al[59]	34	42.5	20	25.0	17	21.2	4	5.0	5	6.2	80	100
Brunqell, Philip J et al[12]	26	49.0	1	2.00	1	2.0	6	11.0	19	36.0	53	100
Soni Arun et al[64]	29	56.0	4	8.0	9	17.0	5	9.5	5	9.5	52	100

According to most of the studies birth asphyxia is the commonest cause of neonatal seizures followed by metabolic or infectious causes. Intracranial hemorrhage constitute small percentage of seizures.

Day of onset of seizures and etiology:

In our study neonatal seizures during the first two days were mostly due to birth asphyxia and onset of seizures due to birth asphyxia during first three days of was seen in 56 cases (98.2%) with highly significant p value of <.0.001.

Seizures due to hypoglycemia begin during second day and peaks on third day and again decreases as the days go on. In our study, out of 18 cases of hypoglycemia6 (33%) began convulsing on 2nd day of life. At the end of first week, seizures are mostly due to neonatal meningitis, which also extends to early second week and later.

After first week, onset of seizures are less likely and are mostly due to meningitis and late onset hypocalcemia in our study. In a study of neonatal seizures by Rose Arthur L et al45, majority of babies with perinatal anoxia convulsed on first day of life (5/10 – 50%), hypoglycemic neonates convulsed on second and third day (5/7 – 71%), majority of neonates with CNS infection convulsed at the end of first week and early second week (9/13 – 69%) and babies with hypocalcemia present with convulsions during first and second day of life (6/28) and again during late first week and second week (19/28).

Birth asphyxia usually presents with seizures within first three days of life, preferably within first 48 hours. Hypoglycemia presents on second and third day, as there is depletion of glycogen stores. Hypocalcemia presents on first and second day if it is early onset hypocalcemia and later i.e., late first week and second week, if it is late onset hypocalcemia. Neonatal meningitis presents with seizures during late first week and second week.

Type of neonatal seizures & Etiology:

In the present study 49% of neonatal seizures with birth asphyxia had subtle type of seizures, followed by GTS in 33.3% & MFC in 7%. In neonates with hypoglycemic seizures, 8 babies had subtle seizures & 6 had GTS. In neonates with meningitis 6 developed subtle seizures and 5 had GTS. There was no correlation between type of neonatal seizures with etiology in our study with $p>0.05$. In study of neonatal seizures compared with EEG studies by Mizrahi EM et al[8] GTS & subtle seizures were likely to be caused by diffuse pathologic processes such as HIE. Clonic seizures, were more likely to be associated with focal or regional lesions such as infarction or ICH with $p=0.0047$.

Birth asphyxia:

Birth asphyxia is the most common cause for neonatal seizures (55.9%) in our study and also in majority of other studies. It can be associated with other metabolic disorders like hypocalcemia and hypoglycemia (4 cases – 7%), as it is a risk factor for those metabolic abnormalities. Most of the asphyxiated newborns are born by vaginal delivery (30) and majority have complications like prolonged second stage of labour (42) and meconium stained liquor (20)

Birth asphyxiated babies developed seizures usually within first 72 hours and more so within first 24 hours and babies with seizures within 24 hours have poor prognosis. Finer MM et al[15] showed that 48% of infants having seizures within 24 hours were significantly handicapped compared to 24% whose seizures began after 24 hours.

Birth asphyxia is staged according to Sarnat as HIE-I, II and III and convulsions are common in HIE-II neonates. In our study 99% of birth asphyxia had HIE-II. In our study 24 babies (42.1%) with birth asphyxia had subtle seizures followed by generalized tonic seizures seen in 16 neonates (28%), focal convulsions are less likely because Kellaway Peter[8], out of 38 asphyxiated babies, 12 (31.6%) had subtle seizures, followed by tonic seizures in 7 (18%).

The risk factors for birth asphyxia are preventable if identified early and proper resuscitation of baby after delivery could reduce the incidence of birth asphyxia significantly.

Metabolic Disorders:

Hypoglycemia:

18 babies had hypoglycemic seizures in our study. 9 were SGA babies, 3 were preterm babies and 6 were term babies i.e., hypoglycemia is more common in low birth weight babies and correlation is statistically significant with $p<0.001$as there is depletion of glycogen storage and inadequate feeding during early post-natal days. The day of onset of hypoglycemic seizures were most commonly seen on second, third and fourth day of life in our study (14 of 18; 77.7%). The diagnosis of hypoglycemia should not be delayed, as it can lead to brain damage.

In a study of hypoglycemia by Lilien Lawrence D et al[51] 41% of hypoglycemic neonates were SGA babies

Hypocalcemia:

In our study 3 babies had hypocalcemia, 2 babies had onset of seizures in 3 days i.e., early onset hypocalcemia, which is due to depleted calcium stores in the baby either due to prematurity and IUGR or complicated hypocalcemia in which other factors like birth asphyxia and maternal diabetes precipitates the hypocalcemia. 1 had late onset hypocalcemia i.e., presented after 3 days of life. This is due to feeding of neonates with phosphate rich milk e.g., cow's milk, formula feeding. Hypocalcemia should be diagnosed early and treated with IV calcium. In a study by Cockburn F et al[30] serum calcium was low in neonates who were top fed, than the babies who were breastfed.

Other metabolic disorders:

Hyponatremia and hypernatremia: One case of hyponatremia associated with neonatal meningitis had seizures in our study. Hyponatremia may result from SIADH following CNS infection and birth asphyxia.

In our study, 2 case of hyperammonemia was diagnosed and was urea cyclic disorder. Other inborn errors of metabolism also present with seizures in the neonatal period usually in the first week of life and should be suspected when all other etiologies are ruled out or if there is a family history.

Intracranial hemorrhage:

In our study, 3 preterm baby presented with seizures diagnosed as IVH on ultrasound cranium and CSF study. Preterm neonates are prone for intraventricular hemorrhage because of fragile blood vessels and ineffective supporting structure for periventricular blood vessels.

CNS infection:

Neonatal meningitis is one of the important causes of neonatal seizures. In our study 13 babies had meningitis (12.7%). 7 were early onset, which presented on or before 7th day remaining were late onset, which presented after 7th day of life. Early onset septicemia is usually acquired from the maternal genital tract or ascending infection through ruptured membranes (PROM). Common organisms in early onset sepsis are, group-B streptococcus, E. Coli and rarely listeria. Late onset is usually due to acquired infection e.g., Staph aureus, streptococcus pneumonia, Klebsiella, E. coli, Pseudomonas. The risk factors are unhygienic practices, handling the babies without hand washing in the NICU etc. Most common organisms grown in CSF culture in our study was Staphylococcus aureus followed by E. coli, one baby had hydrocephalus shown by ultrasound of cranium. Tushar Parikh B et al[65], showed that late onset meningitis is more common than early onset meningitis.

Congenital and developmental disorders:

These are rare causes of neonatal seizures. In our study, 3 patients had seizures due to congenital anomalies, meningomyelocele, hydrocephalus and the other multiple anomalies with microcephaly

Mortality:

Mortality in our study was 17.6% (18 cases) and birth asphyxia was the commonest cause seen in 10 cases (55.5%). Mortality in studies by Sandhu Ravneet et al[59] and Ronen Gabriel et al[63] were 11.25% and 9% respectively and birth asphyxia was the commonest cause.

CONCLUSION

Neonatal Seizures typically signal underlying significant neurological disease and represent non-specific response of the immature nervous system to varied insults. Neonatal seizures are unique & distinctive when compared to seizures in adults because of the immaturity of the nervous system and require separate classification.

The recognition of the etiology for the neonatal seizures is often helpful with respect to prognosis and treatment. The most common etiology for neonatal seizures is hypoxic-ischemic encephalopathy. HIE is frequently associated with perinatal complications like prolonged second stage of labour, MSAF and unsafe home deliveries. Most of these are preventable if proper antenatal & perinatal care is given to the mother.

Neonatal seizures themselves in addition to etiology for the seizures, have a significant impact on the developing brain. Therefore, it is critical to recognize neonatal seizures early, at least clinically where continuous video EEG monitoring facilities are not available, and to initiate the treatment.

Hypoglycemia & Hypocalcemia which are one of the commonest causes, should be suspected & detected as early as possible & treatment started, before it can cause any additional brain damage. Hypoglycemic seizures is more common in LBW babies. Treatable causes should be evaluated before standard anticonvulsants.

The time of onset of neonatal seizures, is significantly associated with the etiology (eg: onset of seizures within first three days is significantly associated with birth asphyxia).

Subtle seizures are commonest type of clinical seizure, which is difficult to identify, therefore careful observation of at risk newborns is necessary for the diagnosis.

Meticulous observation, documentation and use of stimulation and restraint manoeuvers will continue to be paramount for the accurate diagnosis of neonatal seizures.

Most of the neonatal seizure are associated with perinatal complications continued advances in perinatal and neonatal medicine may reduce seizure incidence in the future and prevent the neurologic, cognitive and epileptic consequences of neonatal seizures.

SUMMARY

102 babies with neonatal seizures were studied over a period of 6 months. They showed the following results:

- ❖ Neonatal seizures occur more commonly in male babies with male to female ratio 1.5:1.

- ❖ Most neonatal seizures occur in the first week of life (91.7%), more so within first 3 days of life (79.5%). Highest number is seen on first day of life (36.2%).

- ❖ Subtle seizures are the commonest type of seizure (45.1%), followed by generalized tonic (35.4%), multifocal clonic (7.8%), focal clonic type (5.9%) & mixed type of seizures (5.8%).

- ❖ Birth asphyxia is the commonest cause of neonatal seizures (55.9%), followed by hypoglycemia (17.6%), neonatal meningitis (12.7%) and hypocalcemia (2.9%).

- In neonatal seizures due to birth asphyxia, 49% had subtle seizures, 33.3% had GTS. In hypoglycemic seizures, 44.4% had subtle seizures and 33.3% had GTS. In neonatal seizures due to meningitis, 46.15% had subtle seizures and 38.4% had GTS. There was no correlation between types of seizures with etiology in our study.

- Seizures due to birth asphyxia has onset within first four days of life, more so during first 3days (88%) with statistically significant correlation ($p<0.001$). Majority of hypoglycemic seizures occur during second, third and fourth day (77.7%). Seizures due to neonatal meningitis has onset during end of first week and early second week. Hypocalcemia has 2 peaks, one on second day and the other after first week of life.

- Seizures due to birth asphyxia is seen more commonly in term AGA babies, whereas seizures due to hypoglycemia is more common in low birth weight babies i.e. < 2500gm, with highly significant P value of <0.001.

- ❖ Birth asphyxia has many risk factors like prolonged second stage of labour (40/57 of 70.1%), home delivery and commonly seen in term babies.

- ❖ Neonatal meningitis in our study was the third most common cause of seizures (13/102 – 12.7%). Organisms causing meningitis were mostly Enterococcus and CONS which is community acquired or nosocomial acquired. This can be prevented by proper hand washing technique & hygienic delivery.

Mortality in our study was 17.6% (18/102) & birth asphyxia is the leading cause seen in 10 cases (55.5%). In conclusion, the recognition of etiology of neonatal seizures is often helpful with respect to prognosis and treatment. The most common etiology for neonatal seizure is HIE and is frequently associated with perinatal risk factors. Onset of seizures during first 3 days of life has significant correlation with HIE as etiology. Hypoglycemic seizures are more common in LBW babies. Subtle seizures are commonest type of clinical seizures, which is difficult to identify, therefore careful observation of at risk newborns is necessary.